Eur. Cytokine Netw. Vol. 30, n° 2, *June 2019* 39-42

MINI-REVIEW

Role of IL-33 in transplant biology

Ying Jin[1], Deqiang Kong[2], Chen Liu[2], Weihua Gong[2]

[1] Zhejiang University, Second Affiliated Hospital of School of Medicine, Department of Traditional Chinese Medicine & Rehabilitation, Hangzhou City, People's Republic of China
[2] Zhejiang University, Second Affiliated Hospital of School of Medicine, Department of General Surgery, Hangzhou City, People's Republic of China

Correspondence: Weihua Gong, Zhejiang University, Second Affiliated Hospital of School of Medicine, Department of General Surgery, Jiefang Road #88, Hangzhou City, Zhejiang Province 310009, People's Republic of China.: W. Gong
<weihuagong@zju.edu.cn>

Accepted for publication March 28, 2019

To cite this article: Jin Y, Kong D, Liu C, Gong W. Role of IL-33 in transplant biology. *Eur. Cytokine Netw.* 2019; 30(2): 39-42. doi: 10.1684/ecn.2019.0429

ABSTRACT. Since the pro-inflammatory cytokine IL-33 and its receptor (ST2) are closely involved in regulating both innate and adaptive immune responses, it is conceivable that they may play an important role in organ transplantation. IL-33 is broadly expressed by multiple cell types such as fibroblasts, epithelial cells, and endothelial cells. As a strong inducer of type 2 helper T (Th2) cellular immune responses, IL-33 can significantly prolong allograft survival in organ transplantation partially *via* altering gene expression profiles and increasing frequency of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs). Nevertheless, the IL-33 signaling pathway and its underlying mechanisms remain largely undefined in transplant biology. This present mini-review summarizes recent advances in the studies concerning the IL-33/ST2 signaling pathway and the analysis of its biological function in the field transplantation. The literature points to a deleterious role of activation of the IL-33/ST2 signaling pathway, giving rise to ischemia/reperfusion, acute kidney injury and failure, acute heart rejection, as well as liver fibrosis. Under pro-inflammatory conditions, IL-33 expression is upregulated. Alteration of IL-33 levels has been suggested as a biomarker for predicting organ injury and ongoing allogeneic transplant outcome. These studies have deepened our understanding of immunobiological role of IL-33 and its receptor in organ transplantation. Modulation of the IL-33/ST2 signaling pathway might be utilized as a therapeutic target in the clinic.

Key words: IL-33, inflammatory cytokines, organ transplantation

INTRODUCTION

Interleukin-33 (IL-33) as a member of IL-1 superfamily of cytokines was originally identified as a nuclear factor from high endothelial venules [1]. In 2005, Schmitz *et al.* demonstrated that this molecule has a similar structure and signaling pathway with IL-1 cytokines and was therefore named IL-33 [2]. Human IL-33 was localized on chromosome 9 and mouse IL-33 on chromosome 19. They share 55% homology at the amino-acid level. Within the IL-1 family, IL-33 most closely resembles IL-18 [3]. IL-33 mRNA is broadly expressed by multiple organs and cell types in humans and mice. At the protein level, IL-33 is mainly expressed by fibroblasts, epithelial cells, and endothelial cells, particularly in high endothelial venules [3]. The IL-33 receptor was a complex consisting of ST2 and IL-1 receptor accessory protein (IL-1RAcp) [4]. IL-33 exerts its biological effects *via* IL-1 receptor ST2, activating NF-κB and MAP kinases, and driving production of type 2 helper T (Th2) cells-associated cytokines from *in vitro* polarized Th2 cells. In fact, IL-33 has a dual function under normal circumstances. As a nuclear factor intracellular IL-33 is capable of regulating gene transcription. However, it is released extracellularly to play an immunomodulatory role in an autocrine/paracrine manner as tissue cells are damaged or stressed [5].

IL-33, its receptors ST2, and IL-1RAcP are widely expressed, particularly by immune cells such as innate immune cells and T helper 2 (Th2) cells. IL-33 potently elicits Th2 cytokine production and promotes inflammatory events, causing pathogenesis of Th2-related diseases including atopic dermatitis, asthma, anaphylaxis [6]. Intriguingly, IL-33 bears anti-inflammatory and protective effects in cardiovascular diseases such as obesity, atherosclerosis, cardiac remodeling, and type 2 diabetes, preventing progression of these diseases [5]. Various studies have shown that IL-33 plays an essential role in immune regulation of various diseases, especially with autoimmune diseases [7], allergic diseases [8], infection [9-11], tumor [12-14], and cardiovascular diseases [15, 16]. Attempts of our present study are made to analyze the roles of IL-33 signaling pathway in transplant biology, which might shed light on unveiling allogeneic immune responses and transplant tolerance induction.

ROLE OF IL-33 IN CARDIAC TRANSPLANTATION

With respect to chronic rejection of heart transplantation, the main clinical manifestations are progressive

doi: 10.1684/ecn.2019.0429

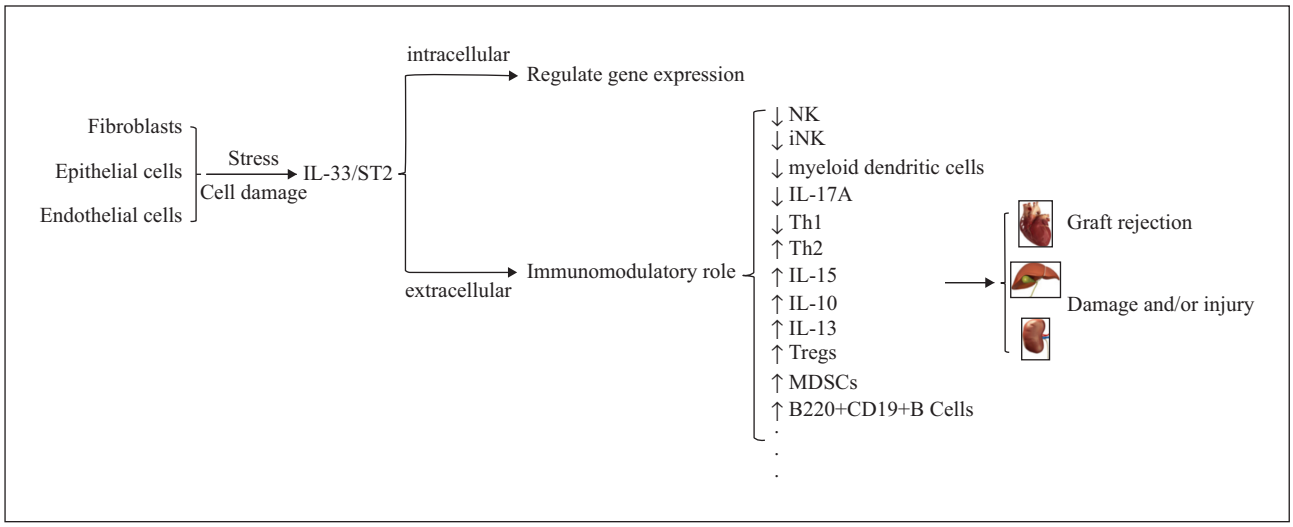

Figure 1
Schematic diagram for the role of interleukin (IL)-33 in the elicitation of cell damage and stress causing graft rejection or organ damage in organ transplantation.

atherosclerosis leading to vascular stenosis obstruction and myocardial ischemic lesions. Both innate and adaptive immune responses can regulate atherogenesis by altering formation and activation of atherosclerotic plaques [17]. In 2008, Miller *et al.* revealed that formation of plaques could be prevented by the administration of IL-33, resulting in a reduction of atherosclerosis development in apolipoprotein E–deficient mice on a high-fat diet [18]. Accumulating evidences showed that the IL-33/sST2 axis was atheroprotective and could be a biomarker for various cardiovascular diseases [15, 16]. Experimental studies exhibited that IL-33 had an important role in either acute or chronic rejection model of mice heart transplantation. It was reported that IL-33 as a strong inducer of Th2 immune responses could significantly prolong allogeneic cardiac graft survival [6]. Each transplant recipient received a rIL-33 (1.0 μg/day) intraperitoneally before the day of transplantation until day 7 posttransplantation. Recipients receiving rIL-33 treatment, allograft survival time was significantly longer (21.7 ± 1.6 days) than that of the control mice (7.2 ± 1.2 days). The underlying mechanism was involved in an augmentation of expression Th2-associated cytokines such as IL-5 and IL-13. The percentage of IL-4 splenic cells was increased, whereas percentage of IFN-gamma splenic cells was decreased [6]. In the chronic rejection model, the transplant recipients treated with IL-33 exhibited evidently longer cardiac allograft survival, which was caused by distinct cytokine profiles and cells. Use of IL-33 led to a decrease of pro-inflammatory cytokine IL-17A production and an increase of IL-5, IL-10, and IL-13. Regulatory T cells and B220+ CD19+ B cells were significantly deposited in the peripheral blood and allografts. In parallel, it was observed that massive myeloid-derived suppressor cells (MDSCs) infiltrated into heart grafts [19]. Further study revealed that pretreatment with IL-33 in heart transplant recipients promoted cardiac allograft survival through tilting a balance from Th1 to Th2 immunity and increasing the number of tolergenic immune cells such as Tregs and MDSCs. Recombinant IL-33 combined with leflunomide significantly prolonged cardiac allograft survival by reducing Th1 type cells and IFN-γ expression and increasing the proportion of Th2 cells, CD4+ Foxp3+ Tregs, and MDSCs (*figure 1*) [20, 21].

ROLE OF IL-33 IN ACUTE KIDNEY INJURY (AKI)

Acute kidney injury (AKI) following liver transplant (LT) is a common event, which may occur in an incidence higher than 50% in some scenarios [22-24]. Serum IL-33 as a pro-inflammatory cytokine is closely associated with inflammatory/injury events and multi-organ dysfunction. It was observed that IL-33 promoted AKI through CD4 T cell-mediated production of CXCL1. Neutralizing IL-33 activity by the administration of a soluble fusion protein ST2 could suppress CD4+ T cellular infiltration within kidney, reduce serum creatinine level, and prevent acute tubular necrosis and apoptosis [25]. A similar clinical observation was achieved, in which a significant elevation of serum IL-33 was found in mice with AKI [26]. Accumulating evidences support the notion that IL-33 can contribute to occurrence of acute kidney injury [27, 28].

ROLE OF IL-33 IN KIDNEY TRANSPLANTATION

Chronic allograft dysfunction (CAD) is the major factor endangering the long-term allograft survival in kidney transplantation. IL-33 was shown to be significantly higher in CAD patients than recipients with stable allograft function and normal controls (healthy volunteers) [29]. Similar experimental studies exhibited that IL-33 was associated with kidney transplantation recipients (KTRs) with CAD. Researchers detected serum IL-33 levels by using an enzyme-linked immunosorbent assay (ELISA) among healthy volunteers, stable KTRs, KTRs with acute rejection (AR), and KTRs with CAD. The findings

revealed that IL-33 was significantly upregulated in the CAD patients compared to the control group. Furthermore, *ex vivo* experimental study showed that IL-33 could induce epithelial to mesenchymal transition (EMT) in a dose-dependent and time-dependent manner and promoted both cellular motility and migration capabilities of HK-2 cells [30]. Further investigation manifested that kidney ischemia-reperfusion injury triggered immediate release of the nuclear alarmin IL-33 in innate immune response and tissue injury. Mice lacking IL-33 displayed a well preservation of renal function and reduction in early tubular cell injury. This protective effect was involved in a decrease of recruitment of natural killer (NK) cells, myeloid dendritic cells, and invariant natural killer T (iNKT) cells [31].

ROLE OF IL-33 IN LIVER ISCHEMIA-REPERFUSION INJURY

Ischemia-reperfusion is an inevitable process for clinical organ procurement and implantation, in which blood supply is reconstructed and subsequently free oxygen radicals and pro-inflammatory cytokines are produced to result in graft injury [32]. IL-33 as an alarmin is released by necrotic cells after tissue damage or acute tissue injury [33-35]. Experimental studies exhibited that IL-33 had a hepatoprotective role in mice during liver ischemia/reperfusion injury. Research data suggested that IL-33 had direct protective effects on hepatocytes, which was associated with activation of NF-κB, p38 MAPK, cyclin D1, and Bcl-2. It limited liver injury and reduced the stimulus for inflammation [36]. A study revealed that lL-33 could be systematically and locally produced in Iiver during the I/R injury process. Pretreatment with lL-33 was therapeutic for hepatic I/R injury, possibly *via* inducing a shift from Th1 to Th2 [35]. Recent study showed that liver ischemia and reperfusion injury caused formation of neutrophil extracellular traps (NET), which contributed to organ damage in liver surgeries. It was reported that IL-33 was released from liver sinusoidal endothelial cells to promote NET formation during liver I/R injury, exacerbating inflammatory cascades and sterile inflammation [35, 37].

ROLE OF IL-33 IN LIVER FIBROSIS AND FAILURE

The major sources of IL-33 in normal liver from both mice and humans were the liver sinusoidal endothelial cells [38]. The role of IL-33 in the development of inflammatory liver diseases has been intensively studied [35, 39]. Both IL-33 and ST2 are elevated in inflammatory liver diseases [40]. Evidence indicated that IL-33 is a critical mediator of hepatic fibrosis *in vivo* and produced in response to chronic hepatocellular stress. IL-33 expression was positively correlated with both ST2 expression and collagen expression in fibrotic livers. As acute liver injury occurred, IL-33 released by damaged hepatocytes and activated hepatic stellate cells might act as an activator of tissue-protective mechanisms. Overexpression of IL-33 was required and sufficient to cause severe liver fibrosis in both humans and mice [38, 39, 41, 42]. IL-33 drove fibrotic livers through activating hepatic stellate cells [43]. Clinical study showed that both chronic and acute hepatic failure was significantly associated with increased serum level of IL-33 and soluble ST2, as evidenced by a significant elevation of peripheral level of these two molecules in chronic and acute liver failure and acute-on-chronic liver failure (ACLF) patients. It is a sign of systemic immune hyperactivation in order to down-regulate inflammation [41]. Clinical or experimental investigations on role of IL-33 in liver transplantation are required in the future since no any data has been shown.

CONCLUSIVE REMARKS

IL-33 and its receptor (ST2) play important roles in the regulation of innate and adaptive immune responses. IL-33 is closely involved in immune tolerance in organ transplantation through altering cytokine profiles and increasing frequencies of Th2 cells, Tregs, and myeloid-derived suppressor cells (MDSCs). All these aforementioned findings could deepen our understanding of biological role of IL-33 and its receptor ST2 in the field of organ transplantation. Modulation of IL-33 bioactivity might be utilized as a therapeutic target in clinic.

Acknowledgements

The project was supported by the National Science Foundation for Outstanding Young Scholars of China (No. 81522006), the Fundamental Research Funds for the Central Universities (2015XZZX004-21), the National Natural Science Foundation of China (No. 81470527, No. 81870306), Zhejiang Provincial 151 Talent Project, and Zhejiang Provincial Outstanding Youth Foundation (No. LR13H020001).

Disclosure. The authors declare that they have no competing interests.

REFERENCES

1. Baekkevold ES, Roussigne M, Yamanaka T, *et al*. Molecular characterization of NF-HEV, a nuclear factor preferentially expressed in human high endothelial venules. *Am J Pathol* 2003; 163 : 69-79.
2. Schmitz J, Owyang A, Oldham E, *et al*. IL-33, an interleukin-1-like cytokine that signals *via* the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines. *Immunity* 2005; 23 : 479-90.
3. Liew FY, Pitman NI, McInnes IB. Disease-associated functions of IL-33: the new kid in the IL-1 family. *Nat Rev Immunol* 2010; 10 : 103-10.
4. Chackerian AA, Oldham ER, Murphy EE, Schmitz J, Pflanz S, Kastelein RA. IL-1 receptor accessory protein and ST2 comprise the IL-33 receptor complex. *J Immunol* 2007; 179 : 2551-5.
5. Miller AM. Role of IL-33 in inflammation and disease. *J Inflamm* 2011; 8 : 22.
6. Yin H, Li XY, Jin XB, *et al*. IL-33 prolongs murine cardiac allograft survival through induction of TH2-type immune deviation. *Transplantation* 2010; 89 : 1189-97.

7. Gajardo Carrasco T, Morales RA, Perez F, *et al*. Alarmin' immunologists: IL-33 as a putative target for modulating t cell-dependent responses. *Front Immunol* 2015; 6 : 232.
8. Louten J, Rankin AL, Li Y, *et al*. Endogenous IL-33 enhances Th2 cytokine production and T-cell responses during allergic airway inflammation. *Int Immunol* 2011; 23 : 307-15.
9. Fanny M, Nascimento M, Baron L, *et al*. The IL-33 receptor ST2 regulates pulmonary inflammation and fibrosis to bleomycin. *Front Immunol* 2018; 9 : 1476.
10. Lopetuso LR, De Salvo C, Pastorelli L, *et al*. IL-33 promotes recovery from acute colitis by inducing miR-320 to stimulate epithelial restitution and repair. *Proc Natl Acad Sci U S A* 2018; 115 : E9362-70.
11. Di Salvo E, Ventura-Spagnolo E, Casciaro M, Navarra M, Gangemi S. IL-33/IL-31 axis: a potential inflammatory pathway. *Mediat Inflamm* 2018; 2018 : 3858032.
12. Serrels B, McGivern N, Canel M, *et al*. IL-33 and ST2 mediate FAK-dependent antitumor immune evasion through transcriptional networks. *Sci Signal* 2017; 10 : pii: eaan8355.
13. Fang M, Li Y, Huang K, *et al*. IL33 promotes colon cancer cell stemness *via* JNK activation and macrophage recruitment. *Cancer Res* 2017; 77 : 2735-45.
14. Chen H, Chen Y, Liu H, Que Y, Zhang X, Zheng F. Integrated expression profiles analysis reveals correlations between the IL-33/ST2 axis and CD8(+) T cells, regulatory T cells, and myeloid-derived suppressor cells in soft tissue sarcoma. *Front Immunol* 2018; 9 : 1179.
15. Altara R, Ghali R, Mallat Z, Cataliotti A, Booz GW, Zouein FA. Conflicting vascular and metabolic impact of the IL-33/sST2 axis. *Cardiovasc Res* 2018; 114 : 1578-94.
16. Ghali R, Altara R, Louch WE, *et al*. IL-33 (interleukin 33)/sST2 (soluble suppression of tumorigenicity 2) axis in hypertension and heart failure. *Hypertension* 2018; 72 : 818-28.
17. Hansson GK, Libby P. The immune response in atherosclerosis: a double-edged sword. *Nat Rev Immunol* 2006; 6 : 508-19.
18. Miller AM, Xu D, Asquith DL, *et al*. IL-33 reduces the development of atherosclerosis. *J Exp Med* 2008; 205 : 339-46.
19. Brunner SM, Schiechl G, Falk W, Schlitt HJ, Geissler EK, Fichtner-Feigl S. Interleukin-33 prolongs allograft survival during chronic cardiac rejection. *Transpl Int* 2011; 24 : 1027-39.
20. Dai C, Lu FN, Jin N, *et al*. Recombinant IL-33 prolongs leflunomide-mediated graft survival by reducing IFN-gamma and expanding CD4(+)Foxp3(+) T cells in concordant heart transplantation. *Lab Investig* 2016; 96 : 820-9.
21. Turnquist HR, Zhao Z, Rosborough BR, *et al*. IL-33 expands suppressive CD11b+ Gr-1(int) and regulatory T cells, including ST2L+ Foxp3+ cells, and mediates regulatory T cell-dependent promotion of cardiac allograft survival. *J Immunol* 2011; 187 : 4598-610.
22. Hilmi IA, Damian D, Al-Khafaji A, *et al*. Acute kidney injury following orthotopic liver transplantation: incidence, risk factors, and effects on patient and graft outcomes. *Br J Anaesth* 2015; 114 : 919-26.
23. Angeli P, Bezinover D, Biancofiore G, *et al*. Acute kidney injury in liver transplant candidates: a position paper on be half of the Liver Intensive Care Group of Europe. *Minerva Anestesiol* 2017; 83 : 88-101.
24. Durand F, Francoz C, Asrani SK, *et al*. Acute kidney injury after liver transplantation. *Transplantation* 2018; 102 : 1636-49.
25. Akcay A, Nguyen Q, He Z, *et al*. IL-33 exacerbates acute kidney injury. *J Am Soc Nephrol* 2011; 22 : 2057-67.
26. Liang H, Xu F, Wen XJ, *et al*. Interleukin-33 signaling contributes to renal fibrosis following ischemia reperfusion. *Eur J Pharmacol* 2017; 812 : 18-27.
27. Yang F, Zhu P, Duan L, Yang L, Wang J. IL33 and kidney disease (review). *Mol Med Rep* 2016; 13 : 3-8.
28. Chen WY, Li LC, Yang JL. Emerging roles of IL-33/ST2 axis in renal diseases. *Int J Mol Sci* 2017; 18. pii: E783.
29. Zhang J, Wang Z, Xu Z, *et al*. The potential role of IL-33 in renal transplant recipients with chronic allograft dysfunction. *Ann Transplant* 2016; 21 : 611-8.
30. Xu Z, Zhao C, Wang Z, *et al*. Interleukin-33 levels are elevated in chronic allograft dysfunction of kidney transplant recipients and promotes epithelial to mesenchymal transition of human kidney (HK-2) cells. *Gene* 2018; 644 : 113-21.
31. Ferhat M, Robin A, Giraud S, *et al*. Endogenous IL-33 contributes to kidney ischemia-reperfusion injury as an alarmin. *J Am Soc Nephrol* 2018; 29 : 1272-88.
32. Liu C, Chen J, Liu B, *et al*. Role of IL-18 in transplant biology. *Eur Cytokine Netw* 2018; 29 : 48-51.
33. Gadani SP, Walsh JT, Smirnov I, Zheng J, Kipnis J. The glia-derived alarmin IL-33 orchestrates the immune response and promotes recovery following CNS injury. *Neuron* 2015; 85 : 703-9.
34. Liew FY, Girard JP, Turnquist HR. Interleukin-33 in health and disease. *Nat Rev Immunol* 2016; 16 : 676-89.
35. Ferhat MH, Robin A, Barbier L, *et al*. The impact of invariant NKT cells in sterile inflammation: the possible contribution of the alarmin/cytokine IL-33. *Front Immunol* 2018; 9 : 2308.
36. Sakai N, Van Sweringen HL, Quillin RC, *et al*. Interleukin-33 is hepatoprotective during liver ischemia/reperfusion in mice. *Hepatology* 2012; 56 : 1468-78.
37. Yazdani HO, Chen HW, Tohme S, *et al*. IL-33 exacerbates liver sterile inflammation by amplifying neutrophil extracellular trap formation. *J Hepatol* 2017;. doi: 10.1016/j.jhep.2017.09.010.
38. Marvie P, Lisbonne M, L'Helgoualc'h A, *et al*. Interleukin-33 overexpression is associated with liver fibrosis in mice and humans. *J Cell Mol Med* 2010; 14 : 1726-39.
39. Kotsiou OS, Gourgoulianis KI, Zarogiannis SG. IL-33/ST2 axis in organ fibrosis. *Front Immunol* 2018; 9 : 2432.
40. Griesenauer B, Paczesny S. The ST2/IL-33 axis in immune cells during inflammatory diseases. *Front Immunol* 2017; 8 : 475.
41. Roth GA, Zimmermann M, Lubsczyk BA, *et al*. Up-regulation of interleukin 33 and soluble ST2 serum levels in liver failure. *J Surg Res* 2010; 163 : e79-83.
42. McHedlidze T, Waldner M, Zopf S, *et al*. Interleukin-33-dependent innate lymphoid cells mediate hepatic fibrosis. *Immunity* 2013; 39 : 357-71.
43. Tan Z, Liu Q, Jiang R, *et al*. Interleukin-33 drives hepatic fibrosis through activation of hepatic stellate cells. *Cell Mol Immunol* 2018; 15 : 388-98.