IL-33 enhances macrophage M2 polarization and protects mice from CVB3-induced viral myocarditis

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A B S T R A C T

Viral myocarditis is the inflammation caused by myocardial virus infection, and the coxsackievirus group B3 virus (CVB3) is the most common pathogen. An efficient therapeutic agent against viral myocarditis is currently unavailable. IL-33, a new member of the IL-1 cytokine superfamily, exhibits potential immunotherapeutic effect against inflammatory and autoimmune diseases. However, the functional role of IL-33 in viral myocarditis has not been investigated. To examine the therapeutic role of IL-33 in viral myocarditis, an IL-33 overexpression plasmid (pDisplay-IL-33) and IL-33 knockdown plasmid (pL3.7-IL-33) were packaged with polyethyleneimine and delivered intravenously at the orbital area of BALB/c male mice after CVB3 infection. Then, myocarditis severity was assessed 7 days after infection. Results showed that IL-33 up-regulation significantly alleviated the severity of viral myocarditis with an increased cardiac contractive function and survival rate. Mechanistic studies demonstrated that IL-33 can stimulate ST2L+ F4/80+ macrophages and ST2L+ CD4+ T cells in cardiac tissue to express IL-4, which is a potent inducer for macrophage M2 polarization. Mice with adoptive transfer of M2 macrophages exhibited less cardiac inflammation and attenuated myocarditis, suggesting the protective role of M2 macrophage in viral myocarditis. Additionally, IL-4 neutralization abolished the IL-33-mediated cardiac functional improvement in myocarditis mice. Collectively, our findings provide a novel therapeutic role for IL-33 in CVB3-induced myocarditis.

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1. Introduction

Viral myocarditis is a principal cause of heart failure in young adults and often progresses to chronic myocarditis, dilated cardiomyopathy, and congestive heart failure [1–4]. Coxsackieviruses are non-enveloped, single-stranded, positive RNA viruses that belong to the Picornaviridae family and Enterovirus genus. Among these viruses, the coxsackievirus B group type 3 (CVB3) is the most common pathogen for viral myocarditis. CVB3 infection mainly involves the synergistic effect of the coxsackievirus–adenovirus receptor and the receptor decay accelerating factor. After entry, the viral RNA is released to the cytoplasm where replication is initiated by the use of host machinery. Two reasons account for the immune damage of CVB3-infected myocardium. One is the direct lysis of infected myocytes through the viral protease 2A-induced dissolution of myocardial cytoskeleton. The other is the excessively activated immune response caused by viral infection [5]. However, an effective method to prevent or treat viral myocarditis is currently unavailable.

Interleukin (IL)-33, which belongs to the IL-1 superfamily, was originally identified as an alarmin in response to cellular damage or stress [6]. IL-33 is constitutively expressed within the nucleus of endothelial and epithelial cells to maintain mechanical barriers [7,8]. The cytokine activates MyD88-dependent signaling pathways in target cells expressing the ST2L/IL-1RACP receptor complex, leading to the production of IL-4, IL-5, IL-10, and IL-13 from eosinophils [9–12], mast cells [13–15], Th2 lymphocytes, and the newly discovered population of type 2 innate lymphoid cells (ILC2) [16,17]. This cytokine reportedly participates in various inflammatory diseases, including allergic rhinitis, ulcerative colitis, allergic asthma, and rheumatoid arthritis [18]. For example, studies using IL-33-deficient mice have revealed the crucial role of IL-33 in the development of experimental allergic rhinitis induced by ragweed pollen [19]. IL-33 is a potent stimulus for skin ILC2s, and the absence of IL-33 signaling decreases skin inflammation in a mouse model of atopic dermatitis [20]. In murine models of RA, IL-33 mRNA has also been detected in the joints of mice that undergo collagen-induced arthritis. Administration of a blocking anti-ST2 antibody at the onset of disease attenuates the severity of CIA and reduces joint destruction [21]. However, the presence of IL-33 in CVB3-induced myocarditis and its regulatory function in viral myocarditis is unknown. In the present study, we manipulated IL-33 expression by polyethylenimine (PEI)-mediated DNA delivery and examined the role of IL-33 in CVB3-induced myocarditis.
2. Materials and methods

2.1. Animals and virus

Six-week-old male BALB/c mice were purchased from the Experimental Animal Center of the Chinese Academy of Sciences (Shanghai, China). All animals were fed in the animal breeding center of Soochow University. Animal experiment operating procedures were in accordance with the guidelines for the Care and Use of Laboratory Animals (Ministry of Health, China, 1998). The guidelines were approved by the Ethics Committee of Soochow University. CVB3 (Nancy strain) were maintained by passage through HeLa cells. Virus titers were determined through a 50% tissue culture infective dose (TCID50) assay of HeLa cells and calculated by the Reed–Muench method.

2.2. CVB3 infection and IL-33 plasmid delivery in mice

Each group contained eight mice except for specific indicating in figure legends. Mice were intraperitoneally injected with 10^3 TCID50 of CVB3 in 0.1 mL of PBS at day 0. At days 1 and 3 after CVB3 infection, each mouse received 50 μg of PEI-packaged DNA plasmid pDisplay-IL-33 or control vector pDisplay for up-regulation, and pLL3.7-IL-33 or control vector pLL3.7 for down-regulation through retro-orbital injection.

2.3. Cardiac IL-33 enzyme-linked immunosorbent assay (ELISA)

Mouse heart tissue was isolated in PBS and then ground with liquid nitrogen. Each sample (100 mg of powdered tissue) was lysed with lysis buffer for 30 min at 4 °C and then centrifuged for 10 min. The supernatants were subjected to ELISA with a mouse IL-33 ELISA kit (eBioscience) in accordance with the manufacturer’s instructions.

2.4. Mouse cardiac echocardiography

Mouse cardiac echocardiography was operated in accordance with the manufacturers’ instructions. In brief, mice underwent intraperitoneal anesthesia and preserved the skin; ultrasonic probes were placed on the manufacturers’ instructions. First-strand complementary DNA was synthesized using 1 μg of total RNA in a 20 μL reaction buffer containing MMLV-RT and oligo (dT) primers (Takara, China). The mixture was incubated at 42 °C for 60 min, 70 °C for 15 min, and then cooled to 4 °C. To detect the expression of genes (TNF-α, iNOS, Fizz-1, and Arginase-1), cDNA was amplified with specific real-time PCR primers by using SYBR green real-time PCR kits (Takara, China). The following mRNA primer sequences were used: iNOS forward primer 5′–CGAAACGCTTACITCCAA–3′, reverse primer 5′–TGACCTTAATGTGGCTGCT–3′; Arginase-1 forward primer 5′–GGTCCCGATGTGACGGAGTC–3′, reverse primer 5′–CGATGCTTTGCGAATAGC–5′; Fizz-1 forward primer 5′–TCCAGTGATCAGGGATC–3′, reverse primer 5′–CCACTCTGAGTTCCAAGA–3′, and TNF-α forward primer 5′–TGTGCTTGGAGCTTACITCCAGA–3′, reverse primer 5′–CTTATGCGGTGATGATGA–3′. The quantified data were analyzed using the 2^(-ΔΔCt) method.

2.6. Adoptive transfer of macrophages

Mouse bone-marrow-derived macrophages (BMDMs) were differentiated in culture for 8 days with 20 ng/mL granulocyte–macrophage colony-stimulating factor (GM-CSF). The BMDMs polarized to M2 with 50 ng/mL IL-33 and 20 ng/mL IL-4 (Invitrogen), and to M1 with 20 ng/mL lipopolysaccharide (LPS) plus 20 ng/mL interferon (IFN)-γ. The purity of the macrophages was measured by FACS. M1 or M2 macrophages (5 × 10^5) were transferred by retro-orbital injection to the recipient mice at 2 days postinfection.

2.7. Cytokine assays

The levels of IL-4, IL-6, and IL-10 of mouse heart homogenates were determined by ELISA (eBioscience) following the manufacturer’s instructions. CK and CK-MB activities were tested by Suzhou Kowloon Hospital Shanghai Jiao Tong University School of Medicine.

2.8. Quantitative real-time PCR

Total RNA samples of myocardial infiltrating macrophages and cultured BMDM were extracted with TRIzol reagent (Takara, China) in accordance with the manufacturer’s instruction. First-strand complementary DNA was synthesized using 1 μg of total RNA in a 20 μL reaction buffer containing MMLV-RT and oligo (dT) primers (Takara, China). The mixture was incubated at 42 °C for 60 min, 70 °C for 15 min, and then cooled to 4 °C. To detect the expression of genes (TNF-α, iNOS, Fizz-1, and Arginase-1), cDNA was amplified with specific real-time PCR primers by using SYBR green real-time PCR kits (Takara, China). The following mRNA primer sequences were used: iNOS forward primer 5′–CGAAACGCTTACITCCAA–3′, reverse primer 5′–TGACCTTAATGTGGCTGCT–3′; Arginase-1 forward primer 5′–GGTCCCGATGTGACGGAGTC–3′, reverse primer 5′–CGATGCTTTGCGAATAGC–5′; Fizz-1 forward primer 5′–TCCAGTGATCAGGGATC–3′, reverse primer 5′–CCACTCTGAGTTCCAAGA–3′, and TNF-α forward primer 5′–TGTGCTTGGAGCTTACITCCAGA–3′, reverse primer 5′–CTTATGCGGTGATGATGA–3′. The quantified data were analyzed using the 2^(-ΔΔCt) method.

2.9. Flow cytometry analysis

Myocardially infiltrated macrophages, splenic macrophages, and BMDMs were stained with FITC anti-CD11b (eBioscience) and PE anti-F4/80 (eBioscience) monoclonal antibodies diluted in 1% FBS in PBS and then measured by flow cytometry on a FACS Calibur cell sorter. The data were analyzed using Flowjo 7.6 Software.

2.10. In vivo cytokine neutralization

Mice were injected intraperitoneally with anti-mIL-4 monoclonal antibodies (R&D Systems, Minneapolis, MN, USA) at a dose of 25 mg/kg at days 1 and 3 after CVB3 infection as previously described.

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**Fig. 1.** Up-regulation and down-regulation of IL-33 in vivo. BALB/c mice were infected with 10^3 TCID50 CVB3 and intravenously injected in the orbital area with 50 μg pDisplay-IL-33, IL-33+pLL3.7, or control vector plasmids (pDisplay or pLL3.7) on days 1 and 3 after infection. IL-33 expression in cardiac tissue was analyzed by ELISA (NC, mice without CVB3 infection). *P < 0.05, **P < 0.01 and ***P < 0.001. Four mice were included at each time point in one group.
Fig. 2. Alleviation of CVB3-induced myocarditis by IL-33 up-regulation. BALB/c mice were infected with CVB3 and intravenously injected in the orbital area with pDisplay-IL-33, pLL3.7-IL-33, or vector plasmid on days 1 and 3 after infection. (A) Body weight changes were monitored daily until day 7 after CVB3 infection. (B) CK and CK-MB activities were also determined at day 7 post infection. (C) Paraffin sections of heart tissues were analyzed by H&E staining. Myocarditis severity was scored using a standard 0–4 scale on the basis of foci of mononuclear infiltration and myocardial necrosis at day 7 after CVB3 infection. (D) Echocardiogram experiments; results of ejection fraction and fractional shortening. (E) Ratio of heart to body weight change at day 7. Results are presented as the means ± SEM of three separate experiments. *P < 0.05, **P < 0.01, and ***P < 0.001. Each group included eight mice. (F) For survival rate detection, each group of mice contained 24–31 as indicated. The survival rate of mice was observed for 7 days. Statistical analysis was performed by survival analyses in software GraphPad Prism 5.0. **P < 0.01, and ***P < 0.001, NC: mice without CVB3 infection.
2.11. Macrophage depletion

Dichloromethylene diphosphonate-loaded liposomes (Cl₂MDP-Lipo) were prepared as previously described [4]. For macrophage depletion, mice were intravenously injected with 200 μL of Cl₂MDP-Lipo 2 days prior to CVB3 infection.

2.12. Statistical analysis

Data are presented as means ± standard error of the mean (SEM). Differences between experimental groups were analyzed for statistical

![Graphs showing mRNA expression of various markers in different conditions.](image-url)
significance using one-way ANOVA test in GraphPad Prism version 5.0 (GraphPad Software Inc.). Statistical significance was considered at \( P < 0.05 \).

3. Results

3.1. Up- and down-regulation of IL-33 in vivo

Recent reports have indicated that IL-33 functions as an alarm signal rapidly released from producing cells upon cellular damage or cellular stress \[8,23,24\]. To examine the role of IL-33 in CVB3-induced myocarditis, up- and down-regulation of IL-33 were conducted by in vivo delivery of PEI-packaged plasmids. Each 50 μg of pDisplay-IL-33 (up-regulation), pLL3.7-IL-33 (down-regulation), or control vector (pDisplay or pLL3.7) was delivered to the mice by orbital intravenous injection at days 1 and 3 after \( 10^3 \text{TCID}_{50} \) CVB3 infection. The dynamic expression of cardiac IL-33 was measured by ELISA daily. The endogenous IL-33 levels increased with viral infection and reached a peak 500 pg/100 mg cardiac tissue at day 5 during acute viral myocarditis (Fig. 1). In the pDisplay-IL-33-treated mice, IL-33 levels increased by twofold (1000 pg/100 mg tissue) compared with that in the CVB3-infected mice 5 days after infection. Moreover, the levels were dramatically higher than that in the control vector pDisplay-treated mice. By contrast, IL-33 levels were reduced in the pLL3.7-IL-33-treated mice compared with the pLL3.7-treated mice. These results suggested that cardiac IL-33 expression was successfully manipulated by the in vivo delivery of PEI-packaged DNA plasmids.

![Fig. 4](image.png)

**Fig. 4.** Alleviation of CVB3-induced myocarditis by M2 macrophages. For macrophage depletion, mice were intravenously injected with 200 μL of CL2MDP-Lipo 2 days prior to CVB3 infection. Bone marrow-derived macrophages were differentiated in culture for 8 days with GM-CSF (20 ng/mL) and polarized to M1 for 24 h with 20 ng/mL IFN-γ and 20 ng/mL LPS, or to M2 macrophages for 24 h with 50 ng/mL murine IL-33. M1 or M2 macrophages (5 × 10^5) were transferred intravenously to the recipient mice 2 days after infection. (A) Spleen macrophage depletion efficiency by CL2MDP-Lipo in CVB3-infected male mice at day 7. (B) Pathological observation of myocarditis in macrophage-depleted male mice at day 7 post-infection and quantified inflammatory scores. (C) Echocardiogram experiments and results of ejection fraction and fractional shortening are shown. Each group involved eight mice. Results are presented as the means ± SEM of three separate experiments. \( *P < 0.05 \), \( **P < 0.01 \) and \( ***P < 0.001 \).
3.2. IL-33 up-regulation alleviates CVB3-induced myocarditis

Next, we examined the effects of IL-33 on CVB3-induced myocarditis by up-regulating and down-regulating IL-33 in mice. Mice underwent continuous body weight loss with myocarditis progress (Fig. 2A). IL-33 up-regulation improved body weight losses, whereas IL-33 down-regulation exacerbated body weight loss. Serum creatine kinase (CK) and CK-MB activity reflects the amount of cardiac damage. Consistently, serological indices of CK and CK-MB activity significantly decreased in the mice treated with pDisplay-IL-33 compared with those treated with pLL3.7-IL-33 or vector (Fig. 2B). This result indicates that IL-33 up-regulation significantly reduced myocardial injury. Importantly, the pDisplay-IL-33-treated mice showed improved histopathology of the heart tissues, with less inflammation and limited necrotic lesions. Meanwhile, myocyte necrosis and immune infiltration were evident in the pLL3.7-IL-33-treated group (Fig. 2C). In vivo ventricular systolic function was measured by fractional shortening (FS) and ejection fraction (EF) using an echocardiography assay. The left ventricular FS (LVFS) in the pDisplay-IL-33-treated mice was significantly higher by 52% compared with that in the control-treated or pLL3.7-IL-33-treated mice. The left ventricular EF (LVEF) was around 80% in the pDisplay-IL-33-treated mice and 40% higher than that in the pLL3.7-IL-33-treated group, indicating that the ventricular function after infection was improved by IL-33 up-regulation (Fig. 2D). In addition, IL-33 up-regulation alleviated the possibility of dilated cardiomyopathy as shown by the ratio of heart to body weight in Fig. 2E. Furthermore, 70.97%(22/31) of the pDisplay-IL-33-treated mice survived during the 7-day infection period. By contrast, only 24.14%(7/29) of the pLL3.7-IL-33-treated mice was not succumbed to death (Fig. 2F). Overall, the above results indicated that IL-33 up-regulation can greatly reduce the severity of CVB3-induced myocarditis in mice.

3.3. IL-33 enhances macrophage polarization in vivo and in vitro

Macrophages play a crucial role in CVB3-induced myocarditis, and differential-subtype macrophages distinctly affect CVB3-induced myocarditis [25,26]. IL-33 has also been shown to effect the macrophages differential-subtype macrophages distinctly affect CVB3-induced myocarditis [28,29]. IL-33 alone may drive the macrophages toward M2 polarization in vitro. Furthermore, IL-33 treatment also successfully reduced the IFN-γ- and LPS-stimulated M1 polarization (Supplementary data 4).

3.4. M2 macrophages were associated with protection against CVB3-induced myocarditis

To confirm the role of macrophage polarization in the pathophysiology of viral myocarditis, we generated M1 macrophages by IFN-γ and LPS induction as well as M2 macrophages by IL-33 in vitro. Mice were intravenously injected with Cl2MDP-Lipo for macrophage depletion as described by a previous study [4]. The frequency of splenic macrophages was reduced from 16.7% to 5.98% 7 days after treatment (Fig. 4A). Then, the mice received the adoptively transferred in vitro stimulated M1 or M2 macrophages 2 days after CVB3 infection. Histological analysis showed that the M1 transfer led to severe myocarditis on day 7 after infection with obvious inflammatory infiltration, whereas the M2 cell transfer and macrophage depletion groups (Cl2MDP-Lipo) did not increase myocarditis (Fig. 4B). Mouse ventricular systolic function was measured by echocardiographic assay. Mouse fractional LVFS and LVEF in the M1 transfer group and Mock depletion group (PBS-Lipo) were lower than those in the M2-like transfer and macrophage depletion groups. This result indicates that the induction of M2 macrophages by...
IL-33 plays a key role in protecting mice against CVB3-induced myocarditis (Fig. 4C).

3.5. ST2L⁺ F4/80⁺ macrophages can be stimulated by IL-33 to secrete IL-4

IL-4 is a potent inducer of M2 macrophage polarization [29]. To determine whether IL-33 could enhance M2 macrophage polarization through IL-4, we assessed the expression of IL-4, IL-6, and IL-10 by ELISA in cardiac tissues after IL-33 up-regulation and down-regulation. Interestingly, the expression of IL-4 and IL-10 but not IL-6 was significantly higher after IL-33 up-regulation than after IL-33 down-regulation (Figs. 5A–C).

ST2L is a component of the IL-33 receptor complex [6]. We analyzed the cell population expressing surface ST2L after CVB3 infection in heart tissue. The percentages of ST2L⁺ F4/80⁺ macrophages and ST2L⁺ CD4⁺ T cells reached 12% and 30%, respectively; however, the percentages of other cell subtypes, such as ST2L⁺ CD8⁺ T cells, ST2L⁺ CD19⁺ B cells, ST2L⁺ CD49b⁺ NK cells, and ST2L⁺ CD3⁺ CD49b⁺ NKT cells, were low and did not significantly change after CVB3 infection (Fig. 5D). To inquire whether IL-4 could be produced by these ST2L⁺ cells after IL-33 stimulation, ST2L⁺ F4/80⁺ macrophages and ST2L⁺ CD4⁺ T cells were isolated and cultured in the presence of IL-33 in vitro. The IL-4 concentration in the culture medium was 350 pg/mL for the ST2L⁺ F4/80⁺ macrophages and 226 pg/mL for the ST2L⁺ CD4⁺ T cells several hours after stimulation (Fig. 5E).

Fig. 5. Decreased function of IL-33 anti-inflammation caused by IL-4 neutralization. Mice were injected intraperitoneally with anti-mIL-4 monoclonal antibodies at a dose of 25 mg/kg at days 1 and 3 after CVB3 infection. (A) Echocardiogram experiments and results of ejection fraction and fractional shortening are shown. (B) Expression of iNOS, TNF-α, Arginase-1, and Fizz-1 in the cardiac macrophages as determined by qPCR at 7 days postinfection. Mice were infected with 10⁷ TCID₅₀ doses of CVB3 and intraperitoneally injected with IL-33 protein at days 1 and 3 after CVB3 infection. Data were collected from a pool of 10 mice for each group. Results are presented as the means ± SEM of three separate experiments. *P < 0.05, **P < 0.01, and ***P < 0.001.
To confirm the role of IL-4 in CVB3-induced myocarditis, we neutralized the mice IL-4 with monoclonal antibodies after IL-33 up-regulation or down-regulation. Compared with the results in Fig. 3A, IL-4 neutralization abolished the cardiac function improvement mediated by IL-33 up-regulation (Fig. 6A). Accordingly, M2 polarization was greatly inhibited by IL-4 inhibition in the IL-33-upregulated group, and Arginase-1 was reduced to undetectable levels. No significant difference in M1 marker expression was noted between the IL-33 up-regulation and down-regulation groups (Fig. 6B). These data again demonstrate that IL-4 is a key factor driving macrophage M2 polarization in vivo.

4. Discussion

One immune response characteristic of viral myocarditis is the inflammation triggered by excessive proinflammatory cytokines during the acute stage of the disease [30]. In the early stage of viral infection, the virus enters the cardiac muscle cells by receptor-mediated endocytosis and then begins replication. As a result, the expression of proinflammatory cytokines and chemokines is increased. During late-stage infection, large numbers of immune cells accumulate in the infected heart tissue and strongly augment the expression of pro-inflammatory cytokines, resulting in massive inflammation and aggravated heart injury [5,31]. The present study demonstrated that although endogenous IL-33 production increased with CVB3 infection, the cytokine still could not completely protect the mice against myocarditis. Nevertheless, IL-33 up-regulation mediated by the delivery of PEI-packaged DNA in vivo protected the mice from CVB3-induced viral myocarditis as indicated by the decreased body weight loss, serological CK and CK-MB levels, and myocardial inflammation, as well as improved left ventricular function and survival rate. These results suggest the therapeutic potential of such method in the treatment of viral myocarditis.

Macrophages play a crucial role in CVB3-induced myocarditis; in particular, differential-phenotype macrophages may generate an opposite inflammatory response [32]. We have shown that M1 macrophages significantly aggravate myocarditis, whereas M2 macrophages alleviate myocardial inflammation [26,33,34]. Macrophages that constitutively express IL-33 receptor and IL-33 preferentially induce the anti-inflammatory function of M2 macrophages in vivo [27,35]. Consistent with the previous report, we observed reduced expression of M1 markers iNOS and TNF-α, as well as elevated expression of Arginase-1 with IL-33 up-regulation, suggesting that IL-33 may protect myocarditis mice by inducing macrophage M2 polarization. In addition, in vivo macrophage depletion and adoptive transfer of M1 cells aggravated CVB3-induced myocarditis. By contrast, the adoptive transfer of IL-33-induced M2 macrophages obviously alleviated myocarditis. These results further confirm the protective role of IL-33-induced M2 macrophages. Although mast cells have been reported play a critical role in the pathogenesis of viral myocarditis [36], pathological observation of myocarditis and echocardiogram experiments showed that there was no protective function of bone-marrow derived mast cells in our study by adoptive transfer. Nevertheless, we still could not exclude the function of other type cells which may be involved in the viral myocarditis.

We also explored the mechanism by which the element induces M2 differentiation. IL-4 is produced by various innate cells, including non-B non-T cells, mast cells, basophils, eosinophils, NK/T cells, and even macrophages themselves [37] and is a potent stimulator of M2 macrophage polarization [38–41]. Our results indicated that in cardiac tissue ST2L + F4/80 + macrophages or ST2L + CD4 + T cells is the main source of IL-4 with IL-33 up-regulation. We further confirmed the role of IL-4 in CVB3-induced myocarditis by IL-4 neutralizing antibody. Neutralization of IL-4 after IL-33 up-regulation or knockdown treatment in CVB3-infected mice reduced the levels of M2 markers (Fizz-1 and Arginase-1) and increased the expression of M1 markers (iNOS and TNF-α), which again prove IL-4 serve as a mediator of macrophage M2 polarization.

In summary, we showed for the first time that IL-33 delivery in vivo can abrogate CVB3-induced myocardial inflammation and alleviate myocarditis severity. IL-33 stimulates the cardiac ST2L + F4/80 + macrophages and ST2L + CD4 + T cells IL-4 expression, which subsequently promotes macrophage M2 polarization and accounts for the suppression of CVB3-induced inflammatory response. Therefore, our findings indicate that IL-33 may be a potential option for viral myocarditis treatment.

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Disclosure

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References


