Review

Cardiology Discovery 心血管病探索（英文）

OPEN

Role of T Cells in Viral and Immune-mediated Myocarditis

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Abstract

Myocarditis is characterized by inflammatory cell infiltration into the myocardium and a high risk of deteriorating cardiac function with a heterogeneous etiology. Both viral- and myosin-induced myocarditis experimental models are used to mimic myocarditis in humans. Here, coxsackie virus B3-induced and non-virus-induced myocarditis models and data obtained in clinical studies were reviewed. Experimental murine myocarditis following immunization with α-myosin together with complete Freund adjuvant represents the classical immune-mediated model. T helper 1 (Th1) and Th2 pathways and important cytokines are involved in the autoimmunity of myocarditis, and the dynamic balance between Th17 and regulatory T cell seems to have an important role in the process of myocarditis. The purpose of this review is to summarize the existing understanding of the immunological mechanisms underlying myocarditis and exploring gaps in knowledge in both animal and human studies, since these mechanistic insights are a critical requirement for the development of novel therapeutic and vaccination strategies.

Keywords: Myocarditis; Immunity; T cells; Animal models; Clinical study

1. Introduction

Myocarditis represents an inflammation of the heart muscle caused by a group of heterogeneous factors, mainly viral, toxic, or immune-mediated, either confined to the heart or in the context of systemic immune-mediated diseases.[1–3] The roles of genetic background, specific viruses, and immunity reactions are still not perfectly known. Animal models were adopted to mimic the pathological process of myocarditis in humans, to reveal the complexity of the disease. Thus far, the etiopathogenetic process of myocarditis points to an autoimmune reaction, in addition to polygenic immunogenetic background and environmental triggers, both in the acute and chronic phases. The role of cardiac autoantibodies is established and relevant,[4–61] but the contribution of T cells is largely unexplored. In this review, we focus on T cell-mediated mechanisms in myocarditis development, by looking into viral, especially coxsackie virus B (CVB)-infected experimental models and autoimmune myosin-induced models, and the T helper 1 (Th1) and Th2 pathways and their interaction. Furthermore, we reviewed the literature on patients with myocarditis and, most recently, the findings on Th17 cells.

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2. Viral myocarditis

2.1. CVB and human myocarditis

Although various etiologies have been implicated in myocarditis, enteroviruses, specifically CVB serotypes, were first identified as the etiological agents in human myocarditis.[62] In 1956, De Jager and Van Creveld[63] reported for the first time an association between CVB4 and a fatal neonatal myocarditis. The frequency of myocardial enteroviral infection has been estimated to account for up to 30%–50% of cases with infectious etiology,[64] and CVB3 represents the classical pathogen for studying animal experimental myocarditis.

Active viral replication as well as latent viral persistence have been described in the hearts of myocarditis patients.[65] Accordingly, molecular analysis by polymerase chain reaction (PCR) is now considered a gold standard tool for the diagnosis of viral myocarditis.[66] Enteroviral RNA has been identified among patients with acute as well as chronic myocarditis/dilated cardiomyopathy (DCM).[67–69] The causal relationship between enteroviral RNA and acute myocarditis, particularly in children, was confirmed by a meta-analysis.[67]

2.2. Animal models of CVB3

CVB3 represents the classical pathogen that induced experimental myocarditis model, with the Nancy CVB3 strain being the most common virus used to induce myocarditis in mice.[70] Genetic background plays a role, since different mouse strains such as BALB/c, A/J, ABY/SnJ, and C57BL/6 mice used to set up the model, show a different susceptibility to the viral-induced and immune-mediated disease. The 2 main methods to trigger CVB3-induced myocarditis make use of either *in vitro*-passaged or heart-passaged CVB3 viral particles.[71] While the former model infects mice via intraperitoneal injection of cell culture-produced CVB3 viruses, the latter model is triggered by using viral particles collected upon homogenizing a CVB3-infected heart, allowing improved survival, but leading to heart remodeling and progression to DCM. In both models, significant injury to the myocardium can be appreciated before immune infiltration occurs, likely directly mediated by CVB3 infection. CVB3 also triggers both innate and adaptive immune

responses, and there are clear clues for an autoimmune phenomenon in mice infected with CVB3.

Mechanistically, CVB3 couples with coxsackie virus and adenovirus receptor (CAR), decay accelerating factor (DAF), and nucleotide-binding oligomerization domain 2 (NOD2), through the help of tyrosine kinases like Fyn and Abl,[72] enters infected cardiomyocytes [Figure 1]. In humans, cardiomyocytes might express up to 5 proteins, distinct from CAR and DAF, that can act as receptors for CVB3.[73] A pathogenetic mechanism of myocardial injury was demonstrated by Badorff et al[74] in 1999 as caused by the release of protease 2A, coded by CVB3, disrupting the dystrophin cytoskeleton complex.

The innate immune system is triggered by pathogen-associated molecular patterns (PAMP) and damage-associated molecular patterns (DAMP) via toll-like (TLR) and nod-like receptors (NLR), including retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated protein 5 (MDA5), to activate nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). CVB3 can also engage the cell surface TLRs through adaptor MyD88, activating downstream signals such as IL-1 receptor–associated kinases (IRAK)-4.[75] The endosomal degradation of the virus can lead to activation of TLRs, in particular TLR3 and TLR7.[76] Thus, activation of NF-κB and activator protein-1 promotes the inflammatory cytokine cascade. Genetic deletion of innate immune TLR intermediates such as MyD88 or IRAK4, or T-cell receptor (TCR) tyrosine kinase p56lck, can all ameliorate myocardial inflammation and survival despite viral proliferation,[77–80] suggesting an immune-mediated damage.

Synthesis of antiviral cytokines such as type I interferons (IFNs) represents the innate immune defense against CVB3 infection, aiming to inhibit viral replication. Activation of TIR domain-containing adapter-inducing IFN-β (TRIF)-dependent TLR3 has been recognized as crucial for antiviral type I IFN production.[81,82] Interestingly, activation of other NLR and TLR pathways exacerbate myocarditis in CVB3-infected mice, through negative regulation of type I IFN and stimulation of pro-inflammatory cytokines.[75,77,83]

Various innate immune cells including natural killer (NK) cells, macrophages, dendritic cells, neutrophils, NK-T cells, and γδ T cells infiltrate the myocardium and contribute to tissue damage by secreting cytokines.[84–86] Pro-inflammatory cytokines include interleukin (IL)-1β, tumor necrosis factor (TNF)-α, IL-23, IL-5, IL-6, IL-8, IL-4, IL-12, IL-17, and IL-23, while anti-inflammatory cytokines include IL-10,[87] transforming growth factor-β (TGF-β), IL-13, and IFN-γ.[87]

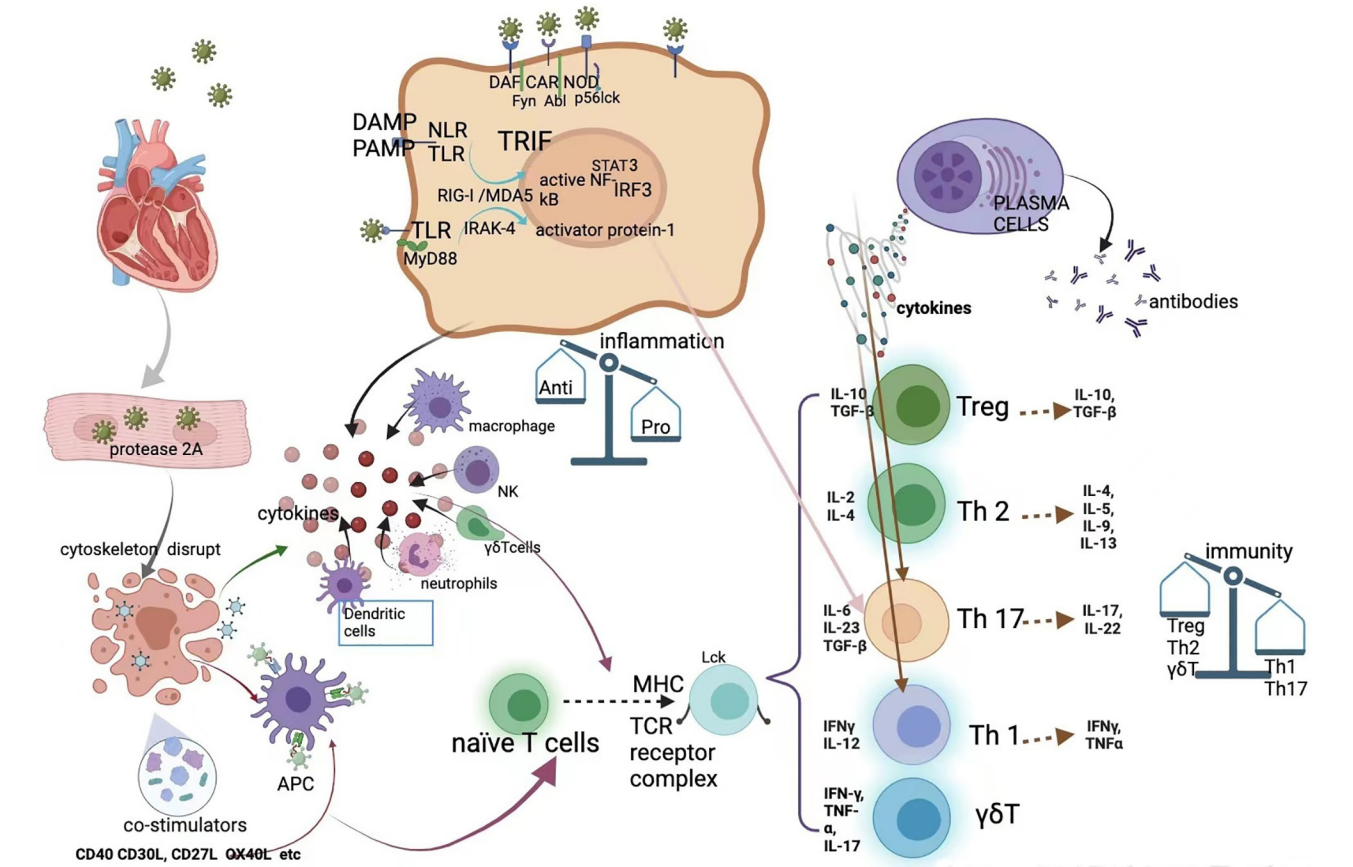

Figure 1: Virus infection and immune reaction mechanisms in CVB3 myocarditis models. CVB3, following its binding to the CAR, enters infected cardiomyocytes, replicates, and causes cell lysis through protease 2A. The PAMP and DAMP pathway triggers an innate immune reaction and causes a series of signaling pathways, releasing both pro- and anti-inflammatory cytokines. Various innate immune cells (NK cells, macrophages, dendritic cells, neutrophils, NK-T cells, γδ T cells) infiltrate the myocardium and contribute to tissue damage, amplifying the vicious circle by secreting additional pro-inflammatory cytokines. APCs capture the lysed cells and viral peptide fragments, with the help of co-stimulators and the cytokine milieu; naive $CD4^+$ T cells can be polarized into Th1, Th2, Th17, or T (Treg) cells. These T cells then control the disease progression through cytokine production. In addition, cell epitopes might have their role in the differentiation of T cells through specific cytokines. APC: Antigen-presenting cell; CAR: Coxsackie virus and adenovirus receptor; CVB3: Coxsackie virus B3; DAF: Decay accelerating factor; DAMP: Damage-associated molecular patterns; IFN: Interferons; IL: Interleukin; IRAK-4: IL-1 receptor-associated kinases-4; IRF3: Interferon regulatory factor; MDA5: Melanoma differentiation-associated protein 5; MHC: Major histocompatibility complex; NF-κB: Nuclear factor κB; NK: Natural killer; NLR: Nod-like receptors; NOD: Nucleotide-binding oligomerization domain; PAMP: Pathogen-associated molecular patterns; RIG-I: Retinoic acid-inducible gene I; STAT3: Signal transducer and activator of transcription 3; TCR: T-cell receptor; TGF-β: Transforming growth factor-β; Th: T helper; TLR: Toll-like receptor; TNF: Tumor necrosis factor; Treg: Regulatory T cell; TRIF: TIR domain-containing adapter-inducing interferon-β.

Virus-associated myocardial injury is essential for the development of cellular immune reactivity; an intact T cell system is required for the induction of myocarditis due to CVB3, as it has been repeatedly demonstrated that various forms of T cell's impairment are protective against virus-induced myocarditis.[88–91] However, heart viral titers in CD8-, CD4-, CD4/CD8-, and TCR-α β-deficient mice were comparable in the first-week post-infection, suggesting that the extent of myocardial injury is mainly determined by immunopathological mechanisms.[92]

The viral peptide fragments are processed in the Golgi apparatus of the host cell and are presented on the cell surface in a major histocompatibility complex (MHC)-restricted manner, which can activate the TCR receptor complex on naive T cells. Further, co-stimulating receptors on T cells interact with their ligands on antigen-presenting cells (APCs), leading to T-cell activation and cytokines production.[93] Indeed, T cells are the key players of cardiac damage.[94] Cardiac myocytes themselves can co-stimulate T cells, inducing cytokine production eventually leading to humoral immune responses, since CVB3-induced myocarditis results in the induction of CD40, CD30L, CD27L, and OX40L on the surface of cardiac myocytes.[95] These ligands are also expressed in murine hearts with chronic ongoing myocarditis caused by CVB3.[96] Blocking the CD40-CD40L interaction by CD40-Ig reduces disease progression in murine CVB3-induced myocarditis.[97] Additionally, Liu et al[79] showed that CVB3 infection *in vivo* requires the expression of a host kinase, Lck, that is essential for T-cell activation.

Naive CD4⁺ T cells can be polarized into Th1, Th2, Th17, or regulatory T (Treg) cells depending on the cytokine milieu. The Th1 pathway, driven by IL-12 and gamma IFN (IFN-γ) is in principle pro-inflammatory and can lead to myocardial infiltration of the heart. However, myocarditis can also be downregulated by an excessive IFN-γ production.[98,99]

Indeed, severe CVB3 myocarditis was observed in the absence of IFN-γ and associated with enhanced IL-1β, IL-4, and TGF-β production.[100] Th2 cell activation is required for CVB3 myocarditis, although the Th2 cytokine IL-13 protects from infection and reduces inflammation.[101]

The Th17 signature cytokine IL-17A was proven dispensable for myocarditis onset but essential for the progression to heart failure,[102] whereas Treg cells have mainly anti-inflammatory effects via secretion of IL-10 and TGF-β.[1–5,102,103]

Studies using CVB3 myocarditis models have indicated that activation of innate immune cells such as macrophages and dendritic cells can indirectly contribute to Th17 cell differentiation.[104,105] Th17 cells can be activated by the NF-κB inflammatory pathway[106,107]; additionally, both IL-23 and IL-6 and the IL-6-activated signal transducer and activator of transcription 3 (STAT3) transcription factor, are considered essential for Th17 cell differentiation, which can also be directly induced by CVB3.[107] The IL-23/Th17 pathway axis is also strongly expressed in CVB3 models.[108]

Treg cells possess a protective role in the CVB3 murine myocarditis model, via IL-10 secretion and activation of pathways including TGF-β, CAR, and thrombospondin-2.[109–111] Indeed, allografted M2 (anti-inflammatory) macrophages led to improvement of viral-induced myocarditis, in association with enhanced levels of Treg cells, and adoptive transfer of a CD4⁺CD25⁺ regulatory like T cell population led to decreased viral load and immune infiltration.[112,113] Additionally, CD4⁺Th9 cells secreting IL-9 play a protective role in disease progression by inhibiting CVB3 replication in the early stages of CVB3-induced myocarditis,[114] while CD4⁺ Th22 cells prevent CVB3-induced chronic myocarditis and its evolution to dilated cardiomyopathy, inhibiting myocardial fibrosis.[115] STAT3 inhibited the NF-KB signaling pathway and reduced inflammatory responses in mice with CVB3-induced myocarditis.[114]

Recent work supports the notions that γδT cells play a prominent role in CVB3-induced myocarditis, inducing apoptosis in cardiac myocytes.[116] Depletion of γδ T cells increases CD4⁺ FoxP3⁺ Treg cell response in CVB3-induced myocarditis.[117] Fas/FasL interactions conferred by γδ T cells regulate the cytokine response to CVB3, promoting a Th1 response.[118] A fraction of these γδ T cells are CD1d-restricted and might trigger γδ TCRs in myocarditis.[119,120] V1 γδ T cells suppress myocardial inflammation, whereas the V4 γδ T cells subset accelerates myocarditis, producing IFN and promoting Th1 responses.[121]

T cells can be indirectly activated by activated B cells, which produce antibodies. CVB3 infection of susceptible humans and mice induces production of autoantibodies to cardiac myosin and other heart antigens, which may be related to the release of cardiac peptides from lysed infected cardiomyocytes or to molecular mimicry (epitope cross-reactivity) between the virus and cardiac proteins. B cells secreting heart-specific autoantibodies may have an influence on immune-mediated myocardial inflammation.[122] Studies on CVB3 infection in B cell-deficient mice indicated that antibodies are not important for the development of myocarditis and disease progression.[123] However, B cells are activated and have strong abilities of antigen presentation and cytokine production; IL-10-producing B cells also promote Th1 and Th17 cell differentiation, and hamper Th2 cell differentiation.[124] B cells form a crucial link between the innate and adaptive immune system. In addition to antigen-specific B cell receptors, B cells also express TLRs. TLR signaling is associated with B cell activation and tolerance and with diverse pathological conditions such as viral myocarditis and septic cardiomyopathy.[125]

Additionally, findings from a study in patients with subacute or chronic myocarditis suggest that CD20⁺ B cells, which induce myocardial damage in mice by activating T cells, and triggering monocyte mobilization, could have a pathophysiological role in inflammatory cardiomyopathy.[126–128]

3. Autoimmunity in myocarditis

Autoimmunity is characterized by defined self-antigens, organ specificity, autoreactive T cells, and autoantibodies that can transfer disease.[129] The finding of autoantibodies supports the involvement of an autoimmune response in many cases of myocarditis in humans and mice, cardiac myosin being the major autoantigen.[14] Pummerer et al[130] reported that mice with myocarditis mounted a polyclonal autoantibody response against α-myosin heavy chain (α-MyHC) (614–629) and another epitope, α-MyHC (334–352). Generally, the reasons for an autoimmune reaction in myocarditis include the following: ineffective thymic deletion or escape of self-reactive T cells; molecular mimicry; and exposure of sequestered autoantigens to the immune system following tissue injury. Lv et al[131] reported that transcripts for α-MyHC are absent in mouse thymic medullary epithelial cells; thus, central tolerance, which specifically eliminates newly developing T cells, cannot identify α-MyHC.[60] Moreover, because α-MyHC cannot be recognized as the body's own antigen, α-MyHC-specific self-reactive T cells cannot undergo "negative selection." Transgenic expression of α-MyHC in thymic epithelium conferred tolerance to cardiac myosin and prevented myocarditis.[131]

Experimental murine myocarditis following immunization with α-myosin together with complete Freund adjuvant represents the classical model.[132] Histological studies of this model defined that myocardial infiltrate contains many macrophages, CD4⁺ T cells, CD8⁺ T cells, and few B cells.[132] CFA contains inactivated *Mycobacterium tuberculosis*, which can stimulate TLR2, TLR4, and TLR9 on host cells.[133] Myosin-induced myocarditis is mediated by CD4⁺ and CD8⁺ T cells, since depletion of CD4⁺ T cells prevents induction of myocarditis,[1–5,103,132,134] but CD4 or CD8 molecules are not required for the induction of autoimmune myocarditis, because both *Cd4*$^{-/-}$ and *Cd8*$^{-/-}$ mice

developed myocarditis.[135] In fact, myosin-reactive T cells are true players of autoimmune myocarditis in this model; these T cells could recognize their self-antigen in the target tissue, with the help of cytokines produced following immunization.[134–136] Adoptive transfer of myosin-induced myocarditis requires class II MHC antigen induction in the heart tissue of the recipients.[137]

Because the active ingredient of CFA stimulates TLRs, Eriksson et al[138] tested whether self-protein-loaded dendritic cells can trigger autoimmunity to a previously identified specific autoantigenic α-myosin peptide. BALB/c (H–2d haplotype) mice were injected with syngeneic, α-MyHC (614–629)-pulsed $CD11c^{+}CD11b^{+}CD80^{+}CD86^{+}$ $CD8^{-}$ MHC class II-positive bone marrow-derived dendritic cells activated with the TLR ligand lipopolysaccharide (LPS) and a stimulatory antibody to CD40. Injection of these dendritic cells induced massive myocarditis in Balb/c mice.[138]

Viruses can infect cardiac cells and induce the innate and adaptive, T cell mediated virus-specific immune response and inflammation necessary to clear infection; however, in genetically predisposed hosts, such response may also induce off target/damaging effects on surrounding cardiac cells fostering post-infectious autoimmune myocarditis, mediated by autoreactive T cells as shown in the CVB3 model of experimental murine myocarditis.[139] Cardiac myosin-induced myocarditis, the best-studied animal model of autoimmune myocarditis, histologically resembles the viral-induced post-infectious autoimmune disease.[33,130,132,134,137] Molecular mimicry between myosin and coxsackie viruses may play a role in myocarditis; immunological mimicry has been suggested to elicit autoantibody-mediated as well as T cell-mediated responses in the presence of a predisposing immunogenetic background.[33,139,140] In principle, persistent viral infection may generate virus proteases and cryptic epitopes even if the virus is not actively replicating, and the autoreactive T cells might be further stimulated by those proteases or epitopes.[140] The association between severe acute respiratory syndrome coronavirus (SARS-CoV) and inflammatory cardiomyopathy is not yet clear, needing further investigation.[141] In addition, it is still unclear whether clinically suspected myocarditis, temporally associated with mRNA vaccines is indeed caused by the vaccine,[142] because temporal association does not prove causation. Nevertheless, a potential mechanism by which the coronavirus disease 2019 (COVID-19) vaccine induces myocarditis is mRNA immune reactivity, that is, the immune response to mRNA might drive the activation of an aberrant innate and acquired immune response. Another potential mechanism might be molecular mimicry between the spike protein of SARS-CoV-2 and cardiac self-antigens. Antibodies directed to SARS-CoV-2 spike glycoproteins might cross-react with structurally similar human protein sequences, including myocardial α-MyHC.[143,144] However, a recent study failed to show significant homology of SARS-CoV-2 spike sequences to myocarditis-associated antigens.[145]

During myocarditis induction, various inflammatory cell subsets infiltrate the heart and produce pro-inflammatory cytokines, which create an amplification loop, further enhancing disease progression.[146] The crucial role of self-reactive $CD4^{+}$ T cells in myocarditis induction is well described,[147] but the underlying mechanisms are still poorly understood. Immunosuppressive strategies are beneficial for some patients with inflammatory

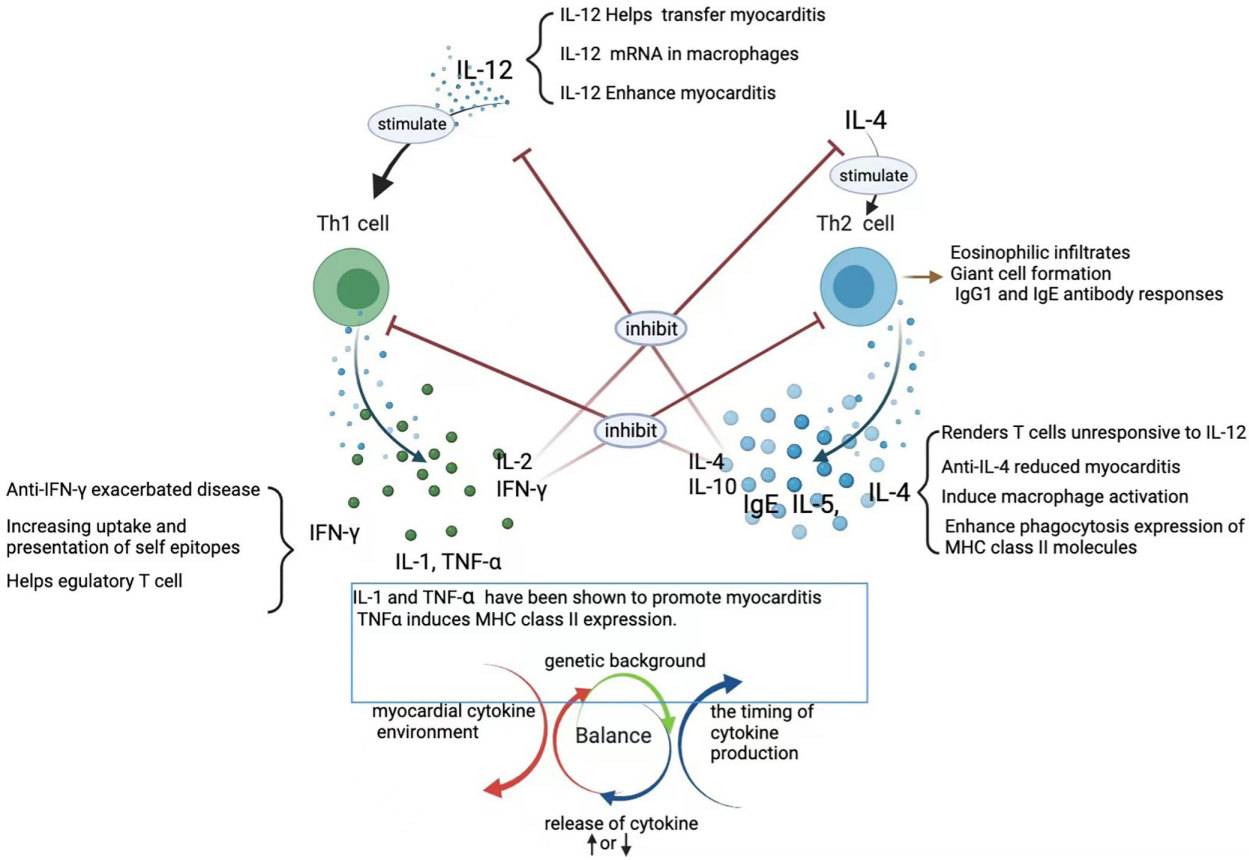

Figure 2: Th1 and Th2 pathways and important cytokines involved in the autoimmunity of myocarditis. Th1 and Th2 are 2 major polarization agents of naive T cells, which play pro- and anti-inflammatory roles, respectively. Th1 is polarized through the stimulation of IL-12, and secrete IL-1, IL-2, IFN-γ, and TNF-α, while Th2 are polarized through IL-4 and secrete IL-4, IL-5, and IL-10. All these cytokines, working in a complicated net, are important to maintain a balanced milieu. The balance between Th1 and Th2 is maintained based on keeping their balance under control of individual genetic background, cytokine milieus, and timing of the cytokine production. IFN: Interferons; Ig: Immunoglobulin; IL: Interleukin; MHC: Major histocompatibility complex; Th: T helper; TNF: Tumor necrosis factor.

DCM and myocarditis without evidence of actively replicating viruses in heart biopsies.[148] T cells, specifically Treg, Th1, and Th17, possess great plasticity, changing their function and phenotype depending on the local milieu in tissue and lymph nodes.[149] Th17 cells facilitate the humoral immune response in human acute viral myocarditis.[150] Some contradictory findings have also been reported; in patients with Chagas' disease, low frequencies of IL-17-producing T cells correlate with more severe symptoms and cardiac dysfunction.[151] IL-17 seems essential for the transition of myocarditis to inflammatory DCM,[102] but IL-17 serum levels normalize within 1 year after the diagnosis, whereas IL-6 and TGF-β remain permanently increased.[102,152] Low serum IL-17 concentrations were also associated with a worse prognosis in patients after acute myocardial infarction.[153]

Class II MHC antigen expression is most likely mediated by IFN-γ, TNF-α, and IL-1. Genetic deletion or blockage of cytokine signaling, including TNF-α, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-1, IL-6, or IL-23 resulted in complete resistance to or amelioration of experimental autoimmune myocarditis (EAM). IL-1 signaling in T cells is required in dendritic cell-mediated Th17 cell differentiation from naive or regulatory precursors and IL-1 synergized with IL-6 and IL-23 to regulate Th17 cell differentiation and maintain cytokine expression in effector Th17 cells.[154–162] The importance of Th1/Th2 immune responses lies in the power of specific cytokines to drive the immune response in an individual or particular animal model toward or away from disease [Figure 2]. Cytokines are important in controlling T cell response to self-antigens and are critical in shifting the immune response toward a Th1 or Th2 pattern [Figure 2].

The classic dichotomist Th1/Th2 model does not provide an accurate representation of the normal immune response.[163,164] IFN-γ-knock-out (KO) mice, IFN-γ-receptor-KO mice, and mice receiving anti-IFN-γ antibody treatment developed more severe inflammatory myocarditis than wild-type strains.[165] In addition, mice deficient in T-bet, a nuclear factor required for Th1 cell differentiation/development, develop more severe myocarditis than wild-type mice.[166] IL-23 is required in the early stages, but is dispensable once GM-CSF-dependent T cell-mediated autoimmunity is established.[161,162] Mice lacking IL-12Rβ1 and STAT4 signals are resistant to myocarditis,[167] whereas exogenous IL-12 caused disease exacerbation.[168] Double IL-17A-KO and IFN-γ-KO mice that lack the responses of Th1 and Th17 after induction of EAM developed severe inflammatory eosinophilic myocarditis, which progressed to DCM, indicating a Th2-biased inflammation leading to eosinophilic myocarditis.[169,170]

The interest in IL-17 function accelerated rapidly with the discovery in 2005, such that IL-17 is the signature cytokine

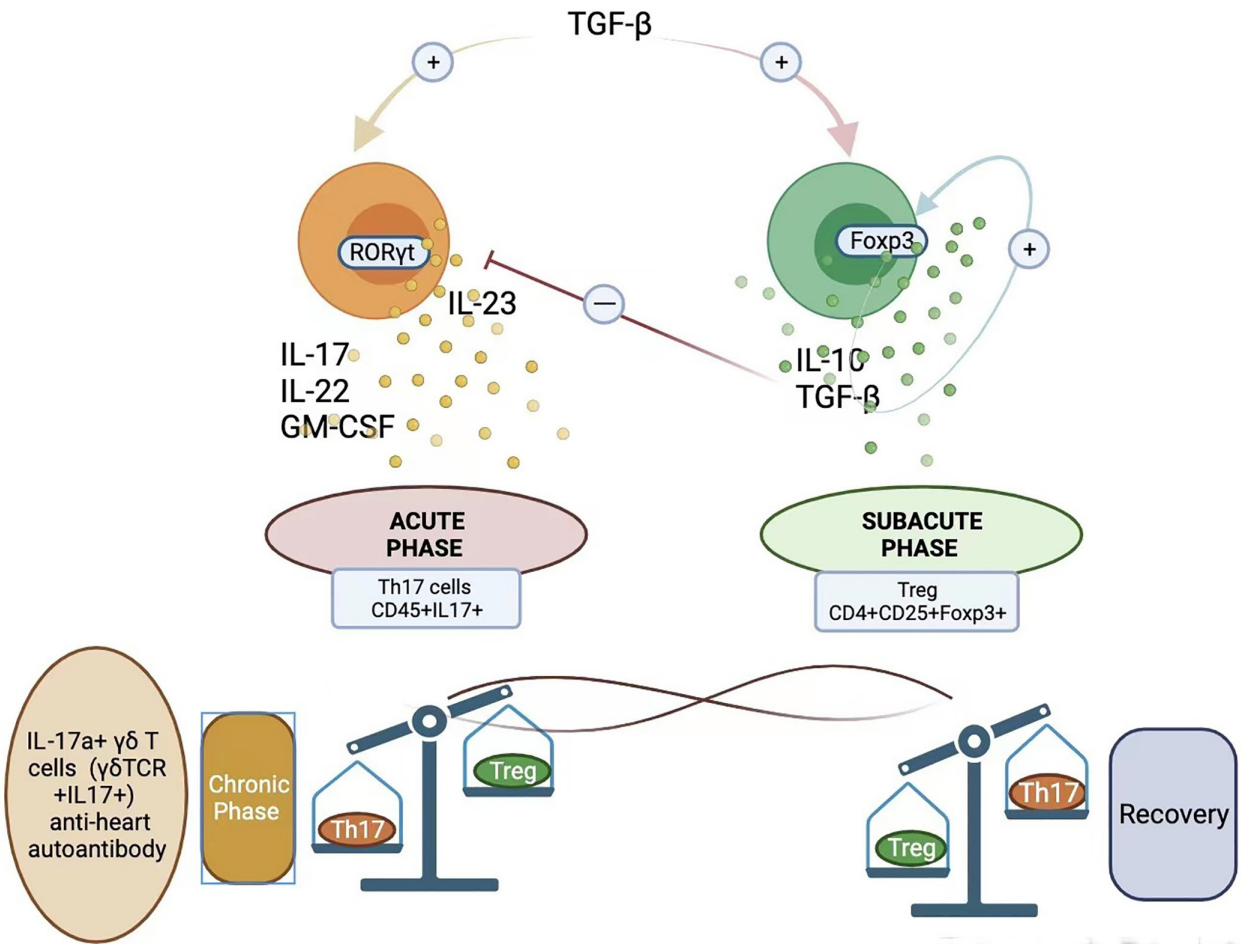

Figure 3: Th17 and Treg dynamic balance in the process of myocarditis. Th17 and Treg cells are polarized with the stimulation of TGF-β and work together to maintain a balanced microenvironment. Th17 cells seem to have an important role in the acute phase of myocarditis, releasing IL-17, IL-22, IL-23, and GM-CSF, which possess a pro-inflammatory function. As the disease progresses, Treg cells take over the role of controlling the development of myocarditis, by releasing IL-1β and, TGF-β, which can inhibit the work of Th17 and produce a balancing anti-inflammatory role. If Th17 cells' function overcomes the Treg inhibition, myocarditis may progress into a chronic phase, leading to dilated myocardiopathy DCM; conversely, if Treg cells adjust the pro-inflammatory environment, the disease progress undergoes healing. DCM: Dilated cardiomyopathy; GM-CSF: Granulocyte-macrophage colony-stimulating factor; IL: Interleukin; RORγt: Retinoid-related orphan receptor gamma t; TCR: T-cell receptor; TGF-β: Transforming growth factor-β; Th: T helper; Treg: Regulatory T cell.

of CD4+ Th17 cells, which are characterized by expression of the "master" transcription factor RAR-related orphan receptor gamma (RORγt) and activated by the IL-12 family cytokine IL-23.[171] The so-called "IL-23-IL-17 axis" was found to be a critical driver of autoimmune disease [Figure 3].[172] In the presence of IL-6 or IL-21 (together with TGF-β), naive CD4+ T cells differentiate into Th17 cells; however, in the absence of pro-inflammatory cytokines, TGF-β drives differentiation into Treg cells.[173] Th17 cells produce IL-17, IL-22, and IL-23; recruit neutrophils; and promote inflammation at the infection site. By contrast, Treg cells produce anti-inflammatory cytokines IL-10 and TGF-β, suppress the activity of a variety of immune cells, and thereby inhibit immune responses.[173] IL-10 can bind to specific IL-10 receptors located on mast cells to prevent the release of inflammatory mediators.[174] IL-10-Ig-containing medium significantly inhibits IL-17 gene expression in IL-1-stimulated spleen cells to restore excessive increase of Th17/Th1 responses in rats with myocarditis.[175] In EAM, modulating the activities of STATs can lead to further suppression of Th17 and Th1 cell differentiation.[139]

4. Th17 and relative pathway cytokines in myocarditis

Tables 1[150–152,176–182] and 2[102,140,183] show a summary of Th17 studies in cardiomyopathy patients and animal models, respectively. Only 3 publications included biopsy-proven acute myocarditis and DCM.[152,181,184]

Noutsias et al[181] stated that no major role could be confirmed for Th17. By using T-PreAmp real-time reverse transcription polymerase chain reaction (RT-PCR), IL-17 was detected in only 3 background endomyocardial biopsy from patients with myocarditis and in 1 background endomyocardial biopsy from a patient with DCM. Conversely, Myers et al[152] reported significantly higher IL-17A in non-recovered 6-month myocarditis/

Table 1

Studies for Th17 among cardiomyopathy patients.

Frist author	Journal	Patients	Phase	EMB	Methods	Results
Wei[176]	*Immunology* 2017	DCM	DCM	No	FACS, ELISA	The circulating CD4+CD25+GARP+ and CD4+CD25+FOX3+ Treg cell frequencies were decreased in patients with DCM. Circulating Th1 and Th17 frequencies were increased in patients with DCM
Rodríguez-Angulo[177]	*BMC Infectious Diseases* 2017	Chagas' disease	Lown classifications	Yes	Multiplexed bead-based immunoassays	IFN- and IL-17 showed the highest percentages of high producers for Lown classification in patients with high risk of sudden death. Interestingly, amiodarone treatment showed a global decrease of high-producer levels
Ouyang[178]	*Central European Journal of Immunology* 2017	VMC	Acute/convalescent	No	ELISA	The plasma IL-17 level in the acute phase VMC patients was higher than that in the healthy control group ($P < 0.01$) and the convalescent phase VMC patients ($P < 0.05$). The level in the convalescent phase patients was higher than that in the healthy control group ($P < 0.05$)
Myers[152]	*Journal of Clinical Investigation Insight* 2016	Acute myocarditis, DCM	Acute/DCM	Yes	FACS, anti-IL-17A heart biopsy staining, ELISA	Significantly elevated IL-17A in non-recovered 6-month myocarditis/DCM blood samples ($n = 5$) *vs.* healthy controls
Kong[179]	*Molecular Medicine Reports* 2014	DCM	DCM	No	FACS	Percentages of the Th17 cells were profoundly increased in the DCM group (2.27% ± 0.59%) as compared with the control group (0.27% ± 0.07%; $P < 0.01$)
Myers[180]	*Journal of the American College of Cardiology* 2012	Myocarditis, DCM, and control	–	No	FACS	Subjects with myocarditis had lower total CD4+, FOXP+ Treg cells than healthy subjects and displayed lower CD4+FOXP3+CD25+ Treg cells than normal controls. Th17 cells were numerically greater in myocarditis and increased further in DCM
Guedes[151]	*PLOS Neglected Tropical Diseases* 2012	Chagas' disease	–	–	FACS	Flow cytometry analysis showed higher CD4(+)IL-17(+) cells in PBMC cultured from patients without or with mild cardiomyopathy, than in patients with moderate or severe cardiomyopathy. All groups of Chagas' disease patients presented the same frequency of CD4(+) CD25(+) Treg cells
Noutsias[181]	*European Journal of Heart Failure* 2011	Acute myocarditis, DCM	–	Yes	RT-PCR	The T cell infiltrates in human inflammatory DCM are characterized by differential expression of functional T cell markers indicating Th1, Treg, and CTLs, while no major role could be confirmed for Th17
Yuan[150]	*Journal of Clinical Immunology* 2010	Acute VMC, DCM after AVM	–	No	FACS	Both frequencies of Th17 and Th1 cells were markedly increased in patients with acute VMC and Th2 in DCM. The expression of RORγt and T-bet mRNAs in patients with acute VMC was higher than that in DCM and healthy groups ($P < 0.01$)
Cunningham[182]	*Journal of Immunology* 2015	Myocarditis/DCM	–	Yes	FACS, immunohistochemistry, ELISA	Reduced CD4+CD25+FoxP3+ Treg cells (0.000,6), elevated Th17 cells (0.000,8) and increased Th17-promoting cytokines (IL-6 and TGF-β). Th1 (IFN-γ+) cells were not significantly elevated

"–" indicates that the data is not mentioned. AVM: Acute viral myocarditis; CTL: Cytotoxic T lymphocytes; DCM: Dilated cardiomyopathy; ELISA: Enzyme-linked immunosorbent assay; EMB: Background endomyocardial biopsy; FACS: Fluorescence-activated cell sorting; GARP: Glycoprotein-A repetitions predominant; IFN: Interferons; IL: Interleukin; PBMC: Peripheral blood mononuclear cell; RORγt: Retinoid-related orphan receptor gamma t; RT-PCR: Reverse transcription polymerase chain reaction; TGF-β: Transforming growth factor-β; Th: T helper; Treg: Regulatory T cell; VMC: Viral myocarditis.

Table 2

Studies for Th17 among myocarditis animal models.

Frist author	Journal	Model	Phase	Methods	Results
Baldeviano[102]	*Circulation Research* 2010	Immunization of mice with myocarditogenic peptide in complete Freund adjuvant	Myocarditis and DCM	Flow cytometry (FACS) and cytokine analysis	IL-17A plays a minimal role during acute myocarditis. IL-17A-deficient mice were protected from post-myocarditis remodeling and did not develop DCM. IL-17A-deficient mice had reduced interstitial myocardial fibrosis, downregulated expression of matrix metalloproteinase-2 and matrix metalloproteinase-9, and decreased gelatinase activity. Treatment of BALB/c mice with anti-IL-17A monoclonal antibody after the onset of myocarditis abrogated myocarditis-induced cardiac fibrosis and preserved ventricular function
Daniels[140]	*Autoimmunity* 2008	Recombinant cardiac myosin fragment induces EAM	–	–	Th1- and Th17-producing cells increase during the acute phase of EAM and could potentially both promote inflammation
Hua[183]	*Circulation* 2020	Myosin heavy chain-α peptides to generate an EAM model	–	Single-cell RNA sequencing	Th17 cells, in which the expression of Hif1a-regulated genes was upregulated, constituted the main T cell population detected at the acute inflammatory phase, whereas regulatory T cells were the main T cell population detected at the subacute inflammatory phase, and gamma delta T cells releasing IL-17 were the main T cell population observed at the myopathy phase. Hif1a expression level correlated with the extent of inflammation

"–" indicates the data is not mentioned. DCM: Dilated cardiomyopathy; EAM: Experimental autoimmune myocarditis; FACS: Fluorescence-activated cell sorting; Hif: Hypoxia-inducible factor; IL: Interleukin; Th: T helper.

DCM blood samples compared to healthy controls. Another author reported, in abstract form, reduced $CD4^+CD25^+FoxP3^+$ Treg cells, elevated Th17 cells, and increased Th17-promoting cytokines (IL-6 and TGF-β) in myocarditis. The $IL\text{-}17A^+$ cells were prevalent in biopsies from human myocarditis; non-recovery was associated with persistence of IL-17A cytokines, and heart failure was associated with elevated Th17 cells in peripheral blood.[182] Other publications on Th17 cells in patients without biopsy-proven myocarditis/DCM showed the same trend.[150,151,176,178,179]

Three papers studied the animal model of myocarditis and DCM. Baldeviano et al[102] reported that IL-17A plays a minimal role during acute myocarditis, but IL-17A-deficient mice were protected from post-myocarditis remodeling and did not develop DCM. Daniels et al[140] found that in myosin-induced EAM, Th1- and Th17-producing cells increase during the acute phase and both of them could potentially promote inflammation. Using single-cell RNA sequencing, Hua et al[183] reported that Th17 cells constituted the main T cell population at the acute inflammatory phase, whereas Treg cells were the main T cell population in the subacute inflammatory phase, and γδ T cells releasing IL-17 were the main T cell population in the chronic myopathy phase. Moreover, the expression level of hypoxia-inducible factor (Hif) correlated with the extent of inflammation.[183]

To summarize, (1) Th1 involvement in the pathological process of myocarditis is still debatable with conflicting results in different experimental models and in patients; (2) Th17 cells are likely involved and their role seems relevant both in the acute and chronic phases, as well as in disease outcome; (3) Treg cells are lower in acute and chronic phases of autoimmune myocarditis; (4) There is lack of information on γδ Th17 cells and Hif-α in human myocarditis.

5. Summary and future perspectives

Various innate and adaptive immune cells are involved in the coxsackie virus murine myocarditis model of virus-associated myocardial injury. Experimental murine myocarditis following immunization with α-myosin together with complete Freund adjuvant represents the classical autoimmune model. Th1 and Th2 pathways and important cytokines are involved in the autoimmune model of myocarditis, and the dynamic balance between Th17 and Treg seems to be playing an important role. Th17 cells are likely relevant both in the acute and chronic phases, as well as in disease outcome, while Treg cells are lower in acute and chronic phases of autoimmune myocarditis.

T-cell activation in myocarditis is due to the interaction of an external environmental trigger and/or an endogenous stimulus within the host's immune system. T cells respond to myocardial antigens in specific inflammatory states such as infection of heart cells and conditions including autoimmune myocarditis, in which self-tolerance to cardiac antigens becomes disturbed. Advanced animal models are required for future research, as there are few publications examining re-infections, co-infections, co-exposures in myocarditis or other autoimmune diseases, and the mechanisms of cardiomyocyte damage mediated by specific viruses. Further exploration of whether the innate response, that is TLR and/or the inflammasome, may influence the adaptive immune response (ie, Th1 or Th2 cells) needs to be undertaken. Furthermore, *in vitro* models with immune cell interactions are needed to facilitate better clinical translation of the animal findings to human disease. Finally, studies on the role of cell-mediated autoimmunity and the immunogenetic background of autoimmune myocarditis and inflammatory cardiomyopathy in patients are warranted.

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Conflicts of interest

None.

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