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REVIEW

Myocarditis and autoimmunity

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ABSTRACT

Introduction: Autoimmune myocarditis may develop due to heterogeneous causes. Myocarditis is often caused by viral infections, but it can also be caused by systemic autoimmune diseases. Immune checkpoint inhibitors and virus vaccines induce immune activation, and they can cause the development of myocarditis, as well as several immune-related adverse events. The development of myocarditis is dependent on the genetic factors of the host, and the major histocompatibility complex (MHC) may be an important determinant of the type and severity of the disease. However, non-MHC immunoregulatory genes may also play a role in determining susceptibility.

Area covered: This review summarizes the current knowledge of the etiology, pathogenesis, diagnosis, and treatment of autoimmune myocarditis with a particular focus on viral infection, autoimmunity, and biomarkers of myocarditis.

Expert opinion: An endomyocardial biopsy may not be the gold standard for the diagnosis of myocarditis. Cardiac magnetic resonance imaging is useful in diagnosing autoimmune myocarditis. Recently identified biomarkers of inflammation and myocyte injury are promising for the diagnosis of myocarditis when measured simultaneously. Future treatments should focus on the appropriate diagnosis of the etiologic agent, as well as on the specific stage of the evolution of immune and inflammatory processes.

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autoantibody; atrial fibrillation; biomarker; COVID-19; immune checkpoint inhibitor; heart failure; vaccine; virus

1. Introduction

Myocarditis, inflammation of the myocardium, may be acute or chronic, and persistent inflammation may progress to cardiomyopathy [1–3]. Myocarditis is often difficult to diagnose clinically because it may present with various signs and symptoms and may mimic other common heart diseases. However, early diagnosis is important since the treatment is different depending on the etiology, and an appropriate therapy can improve clinical course and prevent sequelae to dilated cardiomyopathy. Myocarditis is often caused by viral infections, but it is also associated with systemic autoimmune diseases, bacteria and other microorganisms, and drugs and other substances [1–3]. Persistent inflammation following acute myocarditis may lead to the development of dilated cardiomyopathy or cardiac dysfunction. Cytokines and immune cells that contribute to the innate immunity are involved in the inflammation of the acute stage, and the acquired immunity plays a role in the chronic stage [1–3]. Autoantibodies against various epitopes present on the heart were considered to contribute to the development of the disease [3,4].

Myocarditis is an important contributor to heart disease globally due to cardiomyopathies and sudden death. A writing group of the Global Burden of Diseases, Injuries and Risk Factors systematically reviewed and showed that the burden of myocarditis varied from 0.5% to 4.0% as a cause of heart failure [5]. Since diagnostic tests, such as endomyocardial biopsy and cardiac magnetic resonance (CMR) imaging, are not widely available, the ability to identify myocarditis was limited in cross-sectional studies. Thus, the Global Burden of Diseases report might have underestimated the true rate of myocarditis [5]. Our nationwide study showed that myocarditis was suspected in 24% out of 471 patients with dilated cardiomyopathy who had endomyocardial biopsies [6].

Autoimmune diseases develop as a result of a lack of self-tolerance, due to defective function of the unresponsiveness of the immune system to self-antigens [7,8]. Whatever the cause, acute inflammation may progress to chronic stages and develop fibrosis, the loss of myocardial structure, and a decrease in cardiac function [8–10]. Autoimmune myocarditis may develop alone without any association with the involvement of other organs, as seen in giant-cell myocarditis and eosinophilic myocarditis. However, autoimmune myocarditis might be a response to undetected infectious agents [11]. Furthermore, several systemic autoimmune diseases, including systemic lupus erythematosus (SLE), polymyositis, and Sjögren's syndrome, may be associated with the development of myocarditis [8].

This review summarizes current knowledge on the etiology, pathogenesis, diagnosis, and treatment of autoimmune myocarditis, with a particular focus on viral infection, autoimmunity, and novel biomarkers of myocarditis.

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Article highlights

- Autoimmune myocarditis may develop alone without any association with the involvement of other organs, but it might also be due to undetected infectious agents.
- Viral infection may play an important role in the pathogenesis of autoimmune myocarditis.
- Immune checkpoint inhibitors and virus vaccines can cause the development of autoimmune myocarditis.
- Genetic factors, especially the major histocompatibility complex (MHC), may be an important determinant of the type and severity of myocarditis.
- Endomyocardial biopsy is invasive, and it may not be the gold standard for the diagnosis of myocarditis.
- Dallas criteria for myocarditis are not satisfied in many cases of viral myocarditis.
- Cardiac magnetic resonance imaging is useful in diagnosing autoimmune myocarditis.
- Recently identified biomarkers of inflammation and myocyte damage show promise in the diagnosis of myocarditis when measured simultaneously
- Future treatments should focus on the appropriate diagnosis of the etiologic agent, as well as on the specific stage of the evolution of immune and inflammatory processes.

2. Pathogenesis

2.1. Experimental animal models

2.1.1. Experimental autoimmune myocarditis

Experimental autoimmune myocarditis (EAM) was developed by injection of cardiac myosin or peptides of heavy chain α of cardiac myosin in susceptible strains of mice [12,13]. The development of EAM seems to be dependent on the H2, major histocompatibility complex (MHC) locus of the mouse. The congenic strains of A/J background mice (A/J $H2^a$) and Balb/c ($H2^d$) mice are susceptible, and certain C57BL/10J background mice are also susceptible [14]. The H2-restricted self-peptides are specific to the haplotype and the strain, which demonstrate an MHC preference with translational implications.

2.1.2. Experimental viral myocarditis

A widely used virus for animal models of viral myocarditis in mice is coxsackievirus B3 (CVB3), an enterovirus, the picornaviridae family, that is a cause of viral myocarditis in humans [15–17]. A/J and C57BL/10J mice have been shown to develop acute CVB3 myocarditis, but only A/J mice have been shown to progress to a chronic phase [15,18], suggesting that sustained inflammation progresses to the chronic sequelae of viral myocarditis, which might show a common immunopathogenic process with autoimmune myocarditis [8,19].

We developed animal models using the encephalomyocarditis virus (EMCV), which causes severe heart failure in the acute and chronic stages of the infection in mice [20,21]. Dilatation and hypertrophy have been shown to develop during the chronic stage of the infection in an animal model, as seen in dilated cardiomyopathy [21]. Right ventricular aneurysms, as seen in human arrhythmogenic right ventricular cardiomyopathy, have also been observed in this model [22]. In addition, mural thrombi have been observed in endocardial lesions in the atria, suggesting that acute viral myocarditis carries a risk of thromboembolism [1,23] (Figure 1).

2.2. Genetic background and myocarditis

Development of myocarditis depends on the host genetics as seen in other experimental autoimmune diseases. The H2 determines the severity of myocarditis induced by cardiac myosin or CVB3, but multiple non-MHC immunoregulatory genes contribute in determining susceptibility [25]. We studied EMCV myocarditis in inbred strains of mice with different H2 complexes. Myocardial lesions were frequently seen in BALB/c ($H2^d$), C3H/He ($H2^k$), and DBA/2 mice ($H2^d$), but no pathologic findings were noted in A/J ($H2^a$) or C57BL/6 ($H2^b$) mice [26]. In C3H/He and DBA/2 mice, dilatation and hypertrophy of the heart, in addition to myocardial lesions, persisted up to the eighth month after virus inoculation. This study suggests that MHC genes are critical in the development of viral myocarditis [1,26].

2.3. Cytokines and mast cells

In a previous study, the expression of interleukin (IL)-1β, IL-2, tumor necrosis factor (TNF)-α and interferon (IFN)-γ increased in the heart during the acute stage of EMCV myocarditis. The gene expression of these cytokines decreased gradually but persisted long after inoculation of the virus. The gene expression of IL-1β was high as compared to other cytokines during the chronic stage and correlated with the heart weight and the severity of fibrosis. The mononuclear cells, endothelial cells, and interstitial macrophages were positive for either IL-1β or TNF-α, and the fibroblasts were positive for IL-1β in the heart by an immunohistochemical study. The persistent expression of these cytokines may play an important role in the development of dilated cardiomyopathy [1].

The expression of the genes of chymase of mast cells was increased in the acute to subacute stage of a murine model of EMCV myocarditis, and this activation was associated with myocardial necrosis and fibrosis. The expression of type I procollagen and matrix metalloproteinase (MMP)-9 was also enhanced, suggesting that chymase may contribute to the acute inflammation and the remodeling in acute viral myocarditis [27]. Mice with mast cell deficiency had milder myocarditis than wild-type mice. Activated mast cells release many pro-inflammatory cytokines and fibrogenic mediators such as chymase and tryptase. Moreover, these fibrogenic factors have been shown to increase fibroblasts and may produce stem cell factor (SCF) [28]. SCF can mature and differentiate more mast cell precursors in the heart. Thus, mast cells play a crucial role in viral myocarditis. The functions of mast cells can be controlled using anti-allergic or anti-chemical mediator drugs. In fact, a histamine H1-receptor antagonist improved EMCV myocarditis [29]. Our study suggests that the interaction between SCF and c-kit or the control of mast cell proteases may be promising in the treatment

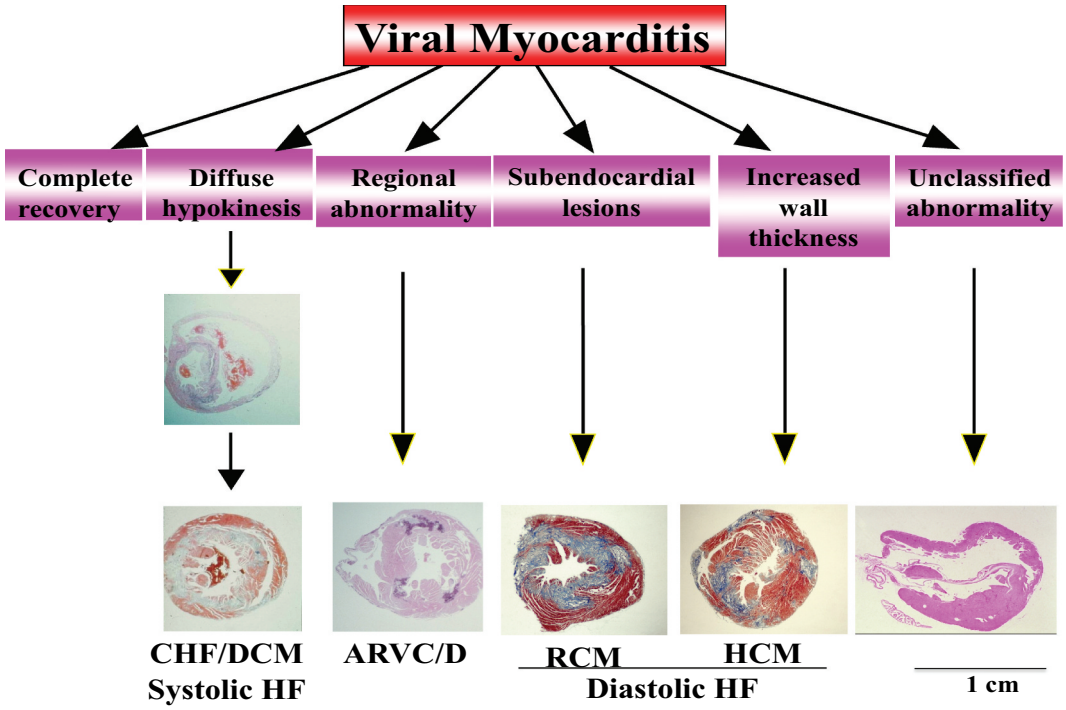

Figure 1. Viral myocarditis in animal models. Viral myocarditis develop lesions similar to those of dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), and arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVC/D). CHF, congestive heart failure; HF, heart failure [24].

of viral myocarditis and prevention of the subsequent dilated cardiomyopathy [29].

2.4. Specific factors triggering/predisposing autoimmune myocarditis

Autoimmune myocarditis seems to be a multifactorial disease. Specific autoimmune process in the myocardium remains to be clarified, but it seems to be host dependent. Myocarditis occurs more frequently in males than in females [8,9,30,31], and the reason is still unknown, but different susceptibilities to TLR4 activation between sexes have been proposed [8,9,30,32].

Mimicry indicates a molecular similarity between the epitopes of the self and non-self and the consequent cross-reactivity with T-cell clones and/or antibodies [33,34]. Heavy chain α of myosin, the isoform specifically expressed in myocytes, is the proposed target of autoimmune myocarditis [35,36]. Myosin and β-adrenergic receptors are other examples of molecular mimicry. The autoantibodies against myosin developed in myocarditis may cross-react with adrenergic receptors, activate the adrenergic system, and may contribute to cardiac damage [37].

Another concept is the exposure of encrypted self-antigens to the immune system [38]. Cardiac myosin is one of the most important targets in myocarditis. Myocardial damage caused by infection, ischemia, or toxic agents may lead to the subsequent exposure of intracellular proteins. This exposure induces an adaptive immune response leading to myocarditis in genetically susceptible individuals [10,25]. Thus, various triggers may develop chronic autoimmune myocarditis.

The genes of human leukocyte antigens (HLAs), the MHC in humans, are some of the most polymorphic genes. The association with specific HLA haplotypes in certain autoimmune diseases is considered to be a result of a higher affinity of certain haplotypes for preserved protein self-products. HLA haplotypes may not be major determinants in the initiation and progression of myocarditis. However, certain associations of HLA haplotypes have been reported, and HLA-DR4, HLA-DR12, DR15, and DRB*0601 are associated with DCM [8].

2.5. Myocarditis associated with autoimmune diseases

The activation of the immune system by self-antigens causes autoimmune-mediated destruction of the tissues and develops systemic autoimmune diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis, and systemic sclerosis [39]. Although accelerated atherosclerosis in patients with autoimmune diseases increases cardiovascular morbidity and mortality [40], increased systemic inflammation and anti-heart autoimmunity may also injure myocardial cells directly [41]. T cells from patients with SLE show the persistent upregulation of co-stimulatory molecules and increase activation and differentiate B cells [42]. B cell regulation is also impaired, the production of autoantibodies and cytokines is increased, and complement is activated, ultimately causing tissue damage by immune-complex deposition [43].

SLE can influence all components of the cardiovascular system. The cardiovascular risk in SLE is more than double that of the general population and is one of the major causes of death [44,45]. The cardiovascular risk of male patients is nearly a 4-fold higher compared to females [46,47].

Myocarditis associated with SLE seems to be mediated by immune-complex deposition, which leads to the activation of complement, inflammation, and myocardial injury [48].

Cardiac involvement of systemic sclerosis varies from 7% to 39%, and this range is linked to both the lack of consensual definition and the wide sensitivity of detecting tools. The most frequent clinical cardiac features may include impaired contractility and relaxation, arrhythmias, myocarditis, and pericardial disease. [49,50]

2.6. Genetics and myocarditis

Recently, the targeted sequencing of cardiomyopathy-associated genes was performed in pediatric patients with biopsy-proven myocarditis and showed that myocarditis patients with phenotypes of dilated cardiomyopathy were characterized by the early onset of heart failure, significant enrichment of likely pathogenic/pathogenic variants, and poor outcomes. These phenotype-specific and age-group-specific findings might be useful for the personalized management of these patients [51].

More recently, genetic variants of genes associated with dilated cardiomyopathy or arrhythmogenic cardiomyopathy were identified in 8% of patients with acute myocarditis. This finding was dominated by truncating variants of titin in patients with reduced ejection fraction of the left ventricle and desmoplakin in those with preserved left ventricular ejection fraction. All-cause mortality in patients with positive genotype tended to be higher compared with those with negative genotypes over a follow-up of 5 years. This study suggests the potential role of sequencing of genes in patients with acute myocarditis and supports the concept that individuals with positive genotype may remain clinically silent until the occurrence of an environmental trigger. These findings may explain some of the heterogeneity in clinical outcomes of acute myocarditis. Thus, genetic analysis may help to stratify the risk and clinical management, including the need for ongoing surveillance and screening of family when genetic variants of cardiomyopathy are present [52].

2.7. Viral myocarditis and autoimmunity

2.7.1. Enteroviruses

Enteroviruses including coxsackievirus, echovirus and poliovirus, and also adenovirus, may cause myocardial necrosis directly, and acute myocarditis develops after myocyte injury (Figure 2). Following myocardial injury, fibrosis replaces injured myocytes, leading to persistent disturbances in cardiac function, and the remaining myocytes develop hypertrophy for compensation [1]. The persistence of the viral genomes of the enteroviruses, adenoviruses, Epstein–Barr virus, hepatitis C virus, human cytomegalovirus, human herpes virus 6, human immunodeficiency virus, and parvovirus B19 has been detected in specimens in myocarditis and cardiomyopathies obtained by endomyocardial biopsy [3,10,53]. However, the presence of viral genomes does not necessarily show the cause of diseases; inflammatory and immune responses are needed to develop myocarditis (Figure 2). The presence of a viral genome alone in the absence of inflammatory cells does not indicate myocarditis [54].

2.7.2. Hepatitis C virus myocarditis

Hepatitis C virus (HCV) infection has been associated with patients diagnosed with arrhythmogenic right ventricular cardiomyopathy, dilated cardiomyopathy, hypertrophic cardiomyopathy, and myocarditis [1,24,55,NaN,57,58]. Conduction disturbances, atrial and ventricular arrhythmias, and QT prolongation have also been associated with HCV infection [57]. We previously showed that CD68-positive monocytes and macrophages were primary targets of HCV infection [58,59]. Antibodies against the HCV core antigen stained mononuclear

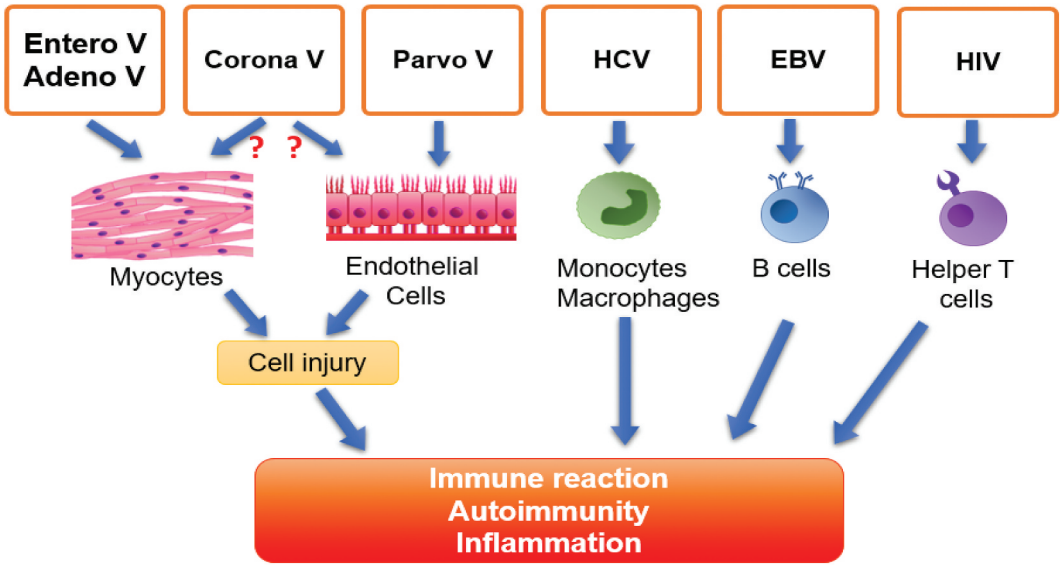

Figure 2. Enteroviruses (Entero V), such as coxsackievirus, echovirus, and poliovirus, and adenoviruses (Adeno V), may cause myocyte necrosis directly, and acute myocarditis follows myocyte injury. However, certain viruses infect inflammatory cells, which may become inflamed and then cause myocyte injury. Corona V, coronaviruses; EBV, Epstein–Barr virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; Parvo V, parvoviruses. ?, needs to be confirmed.

cells in many organs, including the heart, kidney, liver, and bone marrow, but not hepatocytes, myocytes, or globular cells. Antibodies against the NS4 protein of HCV stained peripheral blood mononuclear cells and those of various tissues, confirming that HCV replicates in mononuclear cells [58,59].

The major human MHC codes for the HLA complex, TNF-α, and complements. DQB1*0301 and DRB11101 were shown to be associated with viral clearance in HCV hepatitis, and DQB1 *0401 and DRB1* 0405 were found to be more prevalent in chronic liver disease. DPB10401 and DPB1 *0901 were significantly associated with HCV-associated hypertrophic cardiomyopathy [60,61] (Figure 3). HCV-associated dilated cardiomyopathy was mapped to a non-HLA gene locus spanning from NFKBIL1 to MICA gene loci within the MHC class III – class I boundary region. These results showed that HCV-associated dilated cardiomyopathy had a stronger association with non-HLA genes than with HLA genes. This marked difference in MHC-related disease susceptibility for HCV-associated cardiomyopathies suggests that the development of HCV-associated dilated cardiomyopathy and hypertrophic cardiomyopathy is controlled by different pathogenic mechanisms [62].

2.7.3. COVID-19 and autoimmunity

SARS-CoV-2 infection stimulates immunity and has been reported to be linked to autoimmune diseases, such as SLE, Graves disease, and Kawasaki disease [63,64]. Although the pathogenetic mechanism remains to be clarified, SARS-CoV-2 may stimulate the production of various autoantibodies, which may cause autoimmune diseases [65].

COVID-19 was associated with many cardiac manifestations, including myocarditis, pericarditis, acute coronary syndromes, arrhythmias, and thrombosis [66,67]. Patients with COVID-19 were reported to have cardiac abnormalities in almost all cases in postmortem studies. Cardiac dilatation, fibrosis, hypertrophy of myocytes, amyloidosis, acute ischemia, intracardiac thrombi, pericardial effusion, and myocarditis were observed. SARS-CoV-2 was detected in about half of the heart [68]. However, the Dallas criteria for myocarditis were satisfied in only a small number of cases. Minimal lymphocytic or mononuclear infiltration was observed in 35 cases, and they did not satisfy the Dallas criteria. Therefore, cellular infiltration may not be marked in myocarditis with COVID-19, and, thus, the Dallas criteria are not appropriate for the diagnosis of myocarditis with COVID-19, as observed in HCV myocarditis [1,24,55–59]. In COVID-19, increased interstitial macrophages have been reported in many cases, and lymphocytic myocarditis has been reported in a small number of cases [69]. While the presence of the virus in macrophages has been reported in one case [70], more studies are necessary to confirm this finding.

A strong association has been found between cardiac troponin in the blood and the progression of COVID-19. Circulating cardiac troponin was elevated in 7–28% of patients with COVID-19, suggesting the existence of myocardial injury or myocarditis [71,72]. The mortality rate of patients with elevated levels of circulating troponin was higher than that of patients with normal troponin [73].

We have shown that patients with COVID-19 with no history of cardiovascular disease (CVD) frequently have elevated levels of circulating biomarkers of both cardiac damage, including cardiac troponins and N-terminal pro-brain natriuretic peptide (NT-proBNP), and inflammation, including C-reactive protein (CRP), IL-6, and immunoglobulin-free light chains (FLCs), which are suggestive of myocarditis [74–77]. Circulating troponin T (63%), NT-proBNP (68%), and elevated creatine kinase (43%) were elevated in patients at admission due to COVID-19 [75]. Increased CRP and ferritin suggested

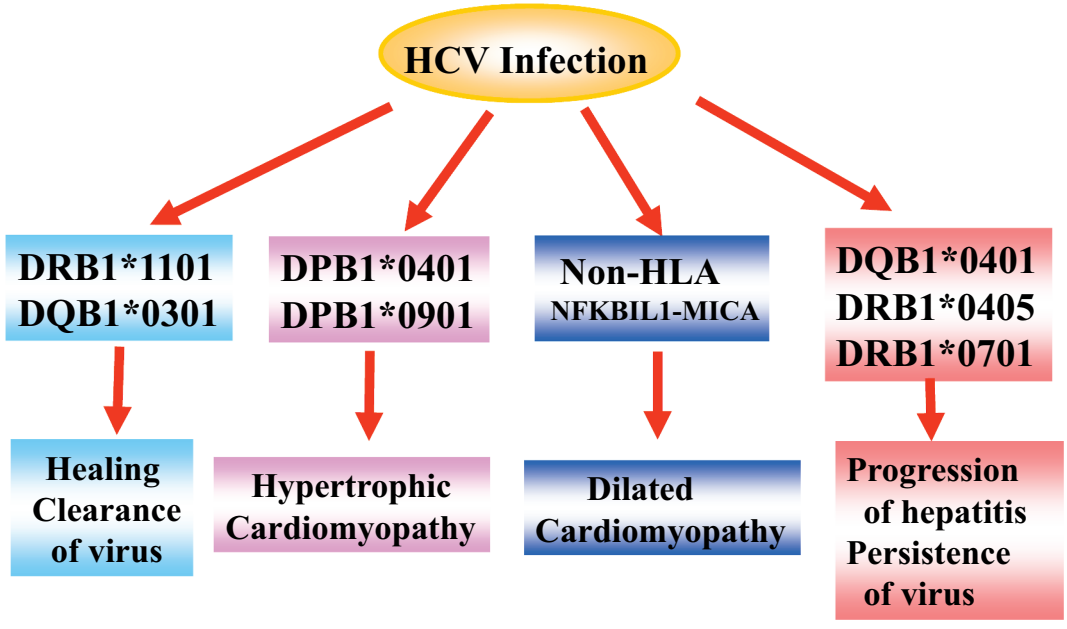

Figure 3. Major histocompatibility complex and HCV myocarditis/cardiomyopathies. In HCV hepatitis, DQB1*0301 and DRB1*1101 were associated with viral clearance. DQB1*0401 and DRB1 *0405 were more prevalent in patients with chronic liver disease. We found that DPB1 *0401 and DPB1*0901 were significantly associated with an increased risk of HCV-associated hypertrophic cardiomyopathy [56,61,62].

that myocardial injury may have been caused by the inflammation [75]. Thus, COVID-19 has been shown to be frequently associated with myocardial injury, suggesting that SARS-CoV-2 causes myocarditis. FLC κ (73%) and λ (80%) were elevated, and IL-6 was increased in 15% [1,72].

Since myocarditis often develops without symptoms, it is difficult to diagnose [78]. Cardiac imaging studies have shown that myocardial inflammation often develops during COVID-19 and can persist in the absence of symptoms [79,80]. However, the symptoms of chest pain and heart failure and abnormal electrocardiograms (ECGs) that can mimic acute coronary syndrome or ventricular arrhythmias can be present [67,81]. Patients with abnormal ECGs were associated with increased mortality [82–84]. Acute myocardial injury in patients with COVID-19 is characterized by elevated cardiac troponins with ST-segment abnormalities on ECGs; however, these findings are not sensitive to detect myocarditis, and their absence does not exclude myocarditis [67,81]. These findings indicate that patients with COVID-19 should receive an ECG, cardiac troponin, and imaging tests (such as echocardiography or CMR) to determine whether they have myocarditis. Circulating biomarkers that indicate cardiac damage and inflammation, such as troponin T and I, CRP, IL-1β, IL-6, and TNF-α, have been found to be associated with increased mortality in patients with COVID-19 [85,86].

We developed an international registry in March 2020 as a collaborative study of the International Society of Cardiomyopathy, Myocarditis and Heart Failure (ISCMF) and the Mayo Clinic to investigate cardiovascular complications of COVID-19. It is important to determine the frequency of myocarditis in patients with COVID-19 because myocarditis may progress to dilated cardiomyopathy [74]. In our study, myocarditis occurred more often in males under the age of 50, and it was also more severe in males [74]. Biomarkers were elevated in patients with COVID-19 without a history of cardiovascular diseases, which may indicate undiagnosed myocarditis. The elevated biomarkers of myocardial damage were correlated with edema on cardiac magnetic resonance images, even when the echocardiogram did not show any abnormalities [79]. Our findings suggest that COVID-19 exacerbates myocarditis that was previously unrecognized and, thus, not diagnosed. This is important because myocarditis is known to progress to dilated cardiomyopathy [1,53]. Our findings suggest that physicians should carefully follow patients' post-COVID-19 infection, checking for the development of dilated cardiomyopathy. Our findings indicate that, even in cases where no abnormalities are found on ECGs or echocardiography, cardiovascular and inflammatory biomarkers may be useful for the diagnosis of myocarditis.

2.8. Myocarditis induced by immune checkpoint inhibitors

We demonstrated in 2001 for the first time that the disruption of the programmed cell death 1 (PD-1) receptor, an inhibitory receptor expressed on T cells, led to fatal myocarditis in mice. PD-1-deficient mice showed marked dilatation of the right and left ventricular cavities of the heart, suggesting that the cause of death was congestive heart failure [87,88] (Figure 4A). Hearts showed severe myocarditis with the deposition of

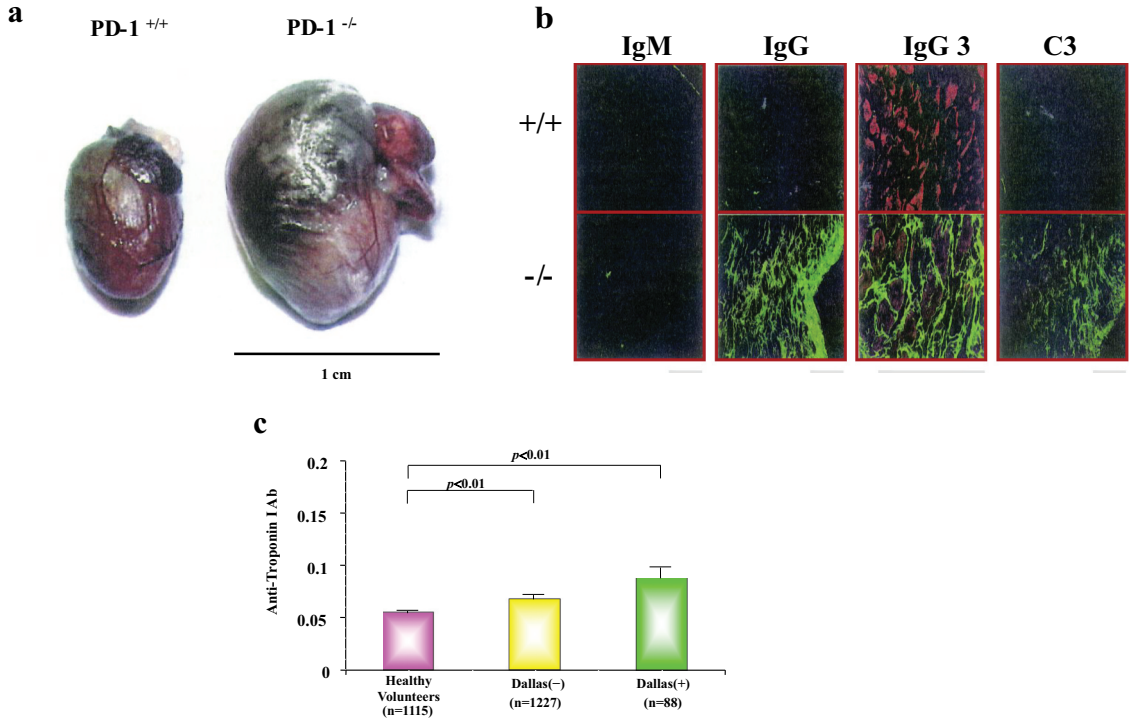

Figure 4. (A) Hearts from PD-1-receptor-deficient (PD-1$^{-/-}$) and wild-type (PD-1$^{+/+}$) mice. (B) Immunofluorescence analysis of hearts from PD-1-receptor-deficient mice. The linear deposition of immunoglobulin G with C3 complement is seen surrounding the cardiomyocytes in the affected hearts [87]. (C). Circulating anti-troponin I antibody in healthy volunteers and in patients whose endomyocardial biopsies satisfied (Dallas +) the Dallas diagnostic criteria for myocarditis versus patients whose biopsies did not satisfy (Dallas –) the Dallas diagnostic criteria for myocarditis [89].

immunoglobulin G on the surface of cardiomyocytes, and the mice had circulating IgG autoantibodies against a 33-kDa antigen [87] (Figure 4B). The protein purified from the heart was identified as cardiac troponin I. Furthermore, exogenously given monoclonal antibodies against cardiac troponin I developed cardiac dilatation and dysfunction in wild-type animals [88].

We found higher titers of the anti-cardiac troponin I antibody in patients with myocarditis whose endomyocardial biopsies satisfied the Dallas criteria than in those whose biopsies did not satisfy them. Furthermore, among those whose biopsies satisfied the Dallas criteria, those with an anti-HCV antibody had higher titers than those without HCV infection. Our study showed that the anti-cardiac troponin I antibody is present in patients with active myocarditis, suggesting that its presence correlates with ongoing inflammation [89] (Figure 4C).

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that block cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), PD-1, and programmed cell death-ligand 1 (PD-L1) and activate the immune system against cancer [90]. Although the efficacy of ICIs has been reported against cancer, ICI therapies cause immune-related adverse events (irAEs) by the dysregulation of the immune system, and they may lead to various organ damage, such as myocarditis, colitis, dermatitis, hepatitis, hypophysitis, and thyroiditis, which are similar to autoimmune diseases [90,91].

Cardiac irAEs have been shown after ICI therapy at a rate of 3.1% in monotherapies and 5.8% in dual or combination therapies [90]. In the WHO's database, frequency of myocarditis induced by ICI ranged from 0.54% for monotherapy to 1.22% for combination therapy [90]. However, myocarditis increased up to 4.5-fold in dual therapies compared to monotherapies [92], suggesting that blocking these two mechanisms may enhance synergistic T-cell autoreactivity in the heart [93]. In early ICI-based cancer trials, myocarditis was not screened prospectively. Furthermore, the diagnosis can be easily missed because the diagnosis of myocarditis is difficult [94]. Recent reports suggest that the incidence of ICI-associated myocarditis is 0.27% to 1.14%, and myocarditis is not frequent, but it is often a lethal complication of ICI therapy [95–97].

A recent study of 2,606 patients at Michigan University conducted serial testing for creatine phosphokinase (CPK), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH) during ICI treatment and showed that ICI-associated myocarditis was diagnosed in 27 patients (1%). Patients with myocarditis showed elevated levels of cardiac troponin T (100%), CPK (89%), ALT (89%), AST (85%), and LDH (93%). Among the noncardiac biomarkers, CPK was shown to be associated with the occurrence of myocarditis and all-cause mortality [98]. In this study, a majority of patients with myocarditis had extra-cardiac irAEs (89%) including hepatitis, myositis, or other diseases. Since ICI-associated myocarditis occurs with other irAEs, patients with increased levels of ALT, AST, or CPK during ICI therapy should undergo promptly further evaluation for ICI myocarditis.

Elevated circulating troponin and electrocardiograms (ECGs) were found in most patients with ICI-associated myocarditis, but half of these patients did not show decreased ejection fractions [96]. The clinical manifestation of ICI-associated myocarditis varies, and fulminant cases have been characterized by early-onset [95,99] and cardiac arrhythmias [96]. A combination of biomarkers, CMR imaging, and late gadolinium enhancement [100] may be helpful for the diagnosis of ICI-associated myocarditis.

Recently, α-myosin was identified as the cognate antigen source for three MHC-I-restricted T-cell receptors (TCRs) derived from mice with fulminant myocarditis. α-Myosin-expanded T cells from the peripheral blood of patients with ICI-myocarditis shared TCR clonotypes with diseased heart and skeletal muscles, indicating that α-myosin may be a clinically important autoantigen in ICI-myocarditis. These studies clarified the critical role of cytotoxic CD8+ T cells, identified a candidate autoantigen in ICI-myocarditis, and gave new insights into the pathogenesis of ICI toxicity [101].

2.9. Vaccine myocarditis

Myocarditis has been shown to be caused by vaccinations [102]. Eight out of 35,188 cases of myocarditis were registered in the Vaccine Adverse Event Reporting System (VAERS) [103]. The incidence of cardiac symptoms and subclinical myocarditis or pericarditis in a study of vaccines of a trivalent influenza vaccine and smallpox, four males were diagnosed with myocarditis, and one female was diagnosed with suspected pericarditis out of 1081 participants [104]. One study on vaccination of smallpox virus in the US military showed that the incidence of myopericarditis was 7.5 times higher than the expected rate in soldiers who received the vaccine [105]. Influenza vaccines have also been associated with myocarditis [106,107].

2.9.1. COVID-19 vaccines and autoimmunity

Myocarditis was reported in individuals after COVID-19 vaccines [102,108,109]. The association of myocarditis with the BNT162b2 (BioNTech/Pfizer) COVID-19 vaccine was studied in healthy members of the US army [110], and myocarditis was diagnosed in 23 people after about 2.8 million mRNA vaccine doses, most of them developed symptoms following the second dose.

By June 2021, 1226 cases of myocarditis had been reported in the US after the administration of more than 296 million doses of mRNA-1273 (Moderna) COVID-19 vaccines [111]. Symptoms usually appeared 3 days after vaccination, and more than 75% of cases occurred after the administration of the second dose; 76% of the cases were men. Myocarditis among males aged 12–29 was 41 cases per million second doses of vaccines and 2.4 per million second doses among those aged over 30.

A systematic review clarified the clinical profiles and cardiac complications post-mRNA COVID-19 vaccines [112]. Myocarditis, pericarditis, and both were the most common adverse events among the 243 cardiac complications reported after mRNA COVID-19 vaccination. Most of the patients were males (92%) with a median age of 21 years. Seventy-four percent of cases with myocarditis had received the

BNT162b2 vaccine, and 88% had received the second dose of the vaccine. Chest pain (96%) and fever (38%) were the most common presentations, and circulating levels of CK-MB (100%), troponin (99.5%), and NT-proBNP (78%) were elevated. ST-segment abnormality was the most common ECGs feature. Decreased left ventricular ejection fraction was seen in 18% by echocardiography. CMR imaging was abnormal in all patients diagnosed with myocarditis. Non-steroidal anti-inflammatory drugs were the most prescribed medications for the management of myocarditis. Some rare cases of Takotsubo cardiomyopathy, myocardial infarction, myocardial infarction with non-obstructive coronary arteries, and isolated tachycardia were also reported following mRNA COVID-19 vaccines. This study showed that myocarditis was the most common adverse cardiac event associated with mRNA COVID-19 vaccines, which presented as chest pain with elevated cardiac biomarkers. Further large-scale observational studies are needed [112].

Another systematic review showed similar findings. Echocardiography showed reduced left ventricular ejection fraction in 44%, hypokinesis of the left ventricular wall in 34%, and pericardial effusion in 22% of patients. The different incidence of reduced ejection fraction compared with the former report may be due to the use of a different definition. The length of hospital stay was 5.5 days. The resolution of symptoms was reported in most of the patients, with only one patient having ongoing heart failure [113].

A comparison of the prognosis between myocarditis associated with mRNA COVID-19 vaccines and viral-infection-related myocarditis has been reported [114]. Over a follow-up period of 180 days, 1 death among 104 patients with post-vaccination myocarditis and 11% mortality among 762 patients with viral myocarditis were identified. One case (1%) of dilated cardiomyopathy and 2% heart failure were identified in the post-vaccination group, compared with 4% and 12% in the viral myocarditis, respectively. An adjusted analysis showed that the post-vaccination myocarditis group had a 92% lower mortality risk. This study showed a significantly lower rate of mortality among individuals with post-vaccination myocarditis compared with those with viral-infection-related myocarditis. The prognosis of myocarditis after mRNA vaccination may be less severe than viral-infection-related myocarditis.

A recent study of 16 young adults and adolescents patients with myocarditis showed increased circulating levels of full-length spike protein unbounded by antibodies, but there was no evidence of excessive antibody or autoantibody production or concomitant viral infection in these patients. These findings are novel, but the pathogenetic role of the spike protein in mRNA vaccine myocarditis remains to be clarified [115].

2.10. Atrial fibrillation and autoimmunity

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and increasing evidence shows that immune and inflammatory mechanisms play a crucial role in its pathogenesis [116,117]. AF increases the risks of stroke, thromboembolism, and heart failure, and thus, it increases morbidity and mortality in cardiovascular diseases [118]. A high incidence of postoperative AF was reported after cardiac surgery, and inflammatory biomarkers including CRP, IL-1β, and IL-6 correlated with the onset of AF [119]. Moreover, randomized controlled trials showed that anti-inflammatory therapies after cardiac surgery reduced the risk of postoperative AF prophylactically. Also, prospective studies suggested that increased levels of CRP predicted the onset of AF in the general population [119]. Histological myocarditis was found in patients with lone AF, and patients with AF exhibited higher nuclear factor (NF)-κB activity and more severe inflammatory cell infiltration than those with sinus rhythm. These observations indicate that local immunologic and inflammatory responses exist within the atrial endocardium in AF [120].

AF was observed in some mice in our experimental animal model of viral myocarditis, and cellular infiltration and myocardial necrosis were accompanied in the atrial myocytes, and atrial thrombus was found in the atrial cavity [23]. These studies suggest that damage to the atrial muscle by inflammation and immune responses may cause AF.

T-cell infiltration has been reported to increase in the hearts of patients with AF [121], and interferon-γ, IL-6, and IL-17A were shown to be independently associated with the AF risk [122]. CD4 T cells were predictive on outcome in patients [123,124]. CCL2 was also associated with the presence of macrophages in the atrial endocardium of patients with AF, who also expressed ICAM-1 and vascular cell adhesion molecule 1 [123,125].

3. Diagnosis

3.1. Imaging

Clinical manifestations of myocarditis are variables including chest pain, dyspnea, fatigue, palpitations, and syncope. ECGs are useful, but they are nonspecific [2]. Laboratory tests include (1) the screening of inflammatory biomarkers including the leukocyte count, CRP, the erythrocyte sedimentation rate, IL-6, and FLCs; (2) markers for myocardial cell necrosis such as high-sensitivity cardiac troponin T and I and creatine kinase-MB; (3) BNP/NT-proBNP testing for the detection of disturbances in ventricular systolic and diastolic functions [1,125]; and (4) serologic/virologic testing where a certain etiology is suspected. CMR images are informative, as they can show myocarditis if inflammatory injury and edema are documented using both T1- and T2-parameters [126]. Recently, CMR imaging has been shown to be useful in the evaluation of patients with autoimmune rheumatic diseases including systemic sclerosis because it can assess cardiac function and tissue characterization simultaneously [127].

3.2. Endomyocardial biopsy

An endomyocardial biopsy, which is performed for evidence of histological inflammation, is invasive and may be subject to sampling bias or error [126]. It should be noted that an endomyocardial biopsy may not be the gold standard for myocarditis because the so-called Dallas criteria, which traditionally represent the definitive diagnosis of myocarditis, are not satisfied in many cases of viral myocarditis [1,24,55–59]. In addition

to the histological and immunohistochemical assessments of biopsy specimens, a polymerase chain reaction or in situ hybridization is recommended to detect viruses, although the clinical significance of viral infection and the causal link between such infections and cardiac injury are still under investigation [54]. The standardization of methods for viral genome identification and quantification is needed. The presence of a viral genome alone in the absence of inflammatory cells is not a diagnostic indicator of myocarditis [54].

3.3. Biomarkers

T lymphocytes are responsible for cell-mediated immunity and may cause damage to the myocardium. T lymphocyte subsets, including CD4+, CD8+, TH17 cells, and Treg cells have been implicated in myocarditis. TH17 cells promoted the development of dilated cardiomyopathy from myocarditis [128–130]. In contrast, Treg cells protected against inflammation, and they are reduced in myocarditis [131,132]. B lymphocytes are responsible for humoral immunity and the production of immunoglobulins, which is an adaptive immune response. Autoantibodies against various antigens of the myocardium are produced in autoimmune myocarditis, including myosin heavy chains, cardiac troponins, β1-adrenergic receptors, Na/K ATPase, and other cardiac proteins [133].

The anti-troponin I antibody was found in PD-1-deficient mice as discussed previously, and the anti-troponin I antibody was detected in patients with myocarditis, especially in those with HCV myocarditis [89]. We found higher titers of the anti-troponin I antibody in patients with myocarditis whose endomyocardial biopsies satisfied the Dallas criteria than in those whose biopsies were negative. Furthermore, among those whose biopsies satisfied the Dallas criteria, patients with HCV infection had higher titers than those without HCV infection. Thus, our study showed that the anti-troponin I antibody is often present in patients with active myocarditis, suggesting that its presence correlates with ongoing inflammation [89]. Several studies showed that anti-cardiac troponin I autoantibodies were found in patients with dilated cardiomyopathy [134]. An increase in exercise capacity was seen after immune-adsorption, and the number of individuals with autoantibodies decreased, though 6 months after this therapeutic intervention, the number increased again [135]. In another study, survival was better in patients with dilated cardiomyopathy compared to ischemic cardiomyopathy, and the presence of anti-troponin I autoantibodies in plasma was associated with improved survival in patients with dilated cardiomyopathy [136]. Further studies are needed to clarify the role of the anti-troponin I antibody in myocarditis.

Recently, we showed that FLCs are novel inflammatory biomarkers [72–77]. NF-κB, a family of transcription factors that bind to the enhancer of the genes of light chains of immunoglobulin, is an important activator of B lymphocytes, and it promotes the production of immunoglobulin light chains. Elevations of certain types of FLCs could be a biomarker of NF-κB signaling and B-lymphocyte activation. A significantly lower FLC κ/λ ratio was observed in patients with myocarditis, and this ratio was an independent prognostic factor for overall survival and showed good diagnostic ability in patients with myocarditis [77].

Macrophages and monocytes have an important effector function in myocarditis [3]. Macrophages may contribute to developing fibrosis leading to adverse cardiac remodeling and finally heart failure. Galectin-3 produced by activated macrophages was shown to mediate this fibrotic process in an experimental model of heart failure [137]. It was also demonstrated to be associated with the inflammatory cells and cardiac fibrosis in patients with myocarditis and cardio-myopathy [138].

Interleukin-33 (IL-33) has been shown to induce type 2 immune responses by activating mast cells, Th1 cells, Th2 cells, T-reg cells, CD8+ cells, and natural killer cells. It has been shown to play a role in autoimmune diseases, infection, inflammation, cancer, and diseases of the central nervous system [139]. IL-33 exerts its effects by binding to the ST2 receptor and others. Circulating sST2 was a decoy receptor for IL-33, and it inhibited the effects of IL-33 by preventing its binding to the membrane-bound isoform, which mediates inflammation. Increased circulating sST2 levels were associated with a poor prognosis in male patients with acute myocarditis [140].

3.3.1. The new FLC biomarker

Increased circulating FLCs have been shown to be biomarkers of B-cell activity in many inflammatory and autoimmune conditions since they emerged as excess byproducts of antibody synthesis by B cells and plasma cells [141]. Polyclonal FLCs have been reported to be a predictor of mortality in the general population [142]. Increased level of FLC κ and the FLC κ/λ ratio was higher in patients with rheumatic diseases than in healthy blood donors [143]. FLCs have been correlated with disease activity in inflammatory and autoimmune diseases, suggesting their role as potential therapeutic targets in these diseases.

We found that circulating and cardiac FLCs were increased in myocarditis and heart failure due to EMCV [76]. We also conducted clinical research, and we found that circulating FLC λ was increased, while the κ/λ ratio was decreased as compared to healthy controls, and we demonstrated that FLC λ and the κ/λ ratio together showed good diagnostic potential for the identification of myocarditis. In addition, the FLC κ/λ ratio could also be used as an independent prognostic factor for overall survival [77].

High concentrations of FLC κ have been reported in patients with HCV, and the κ/λ ratio has been positively correlated with an increase in the severity of HCV-related lymphoproliferative disorder [144]. Furthermore, the κ/λ ratio has been suggested to be useful in the evaluation of therapeutic effects [145]. In our study on FLCs using sera from the US Multicenter Myocarditis Treatment Trial, FLC κ was lower, FLC λ was higher, and the κ/λ ratio was lower in patients with myocarditis, both with and without biopsy confirmation, than in normal volunteers. In patients with HCV infection, these changes were more prominent than in those without infection. HCV infection enhances the production of FLC λ while decreasing FLC κ. Although the mechanisms of these changes remain to be clarified, the detection of FLCs may be helpful in differentiating patients

with HCV infection from those without infection [1,146]. In patients with heart failure, left ventricular end-diastolic and end-systolic diameters, pulmonary arterial pressure, and NT-proBNP positively correlated with FLC λ and negatively correlated with the κ/λ ratio. The left ventricular ejection fraction was also negatively correlated with the κ/λ ratio [1,146].

We measured FLCs and IL-6 in patients with COVID-19. FLC κ and λ were increased in 73% and 80% of patients, respectively, and the frequencies of the increased levels were higher than those of troponin T, NT-proBNP, creatine kinase, and IL-6 [1,75].

In patients with lone AF, circulating FLC κ and λ were significantly different from those in a healthy volunteer group. The area under the curve of the receiver-operating characteristic curve analysis showed that FLC κ and λ were helpful in differentiating patients with AF from healthy volunteers and that the cutoff value of FLC κ or λ may be beneficial in distinguishing between the two groups [116,120]. The mechanism by which FLCs cause AF is not yet fully understood, but the inflammation associated with FLCs may directly induce AF, or FLCs may cause a change in membrane fluidity, which, in turn, could alter ion channel function [116,120].

As discussed above, simultaneous measurement of inflammatory biomarkers and myocardial damage is helpful in diagnosing myocarditis.

3.3.2. MicroRNA

Recently, a microRNA (miRNA) was shown to be a promising biomarker [147]. Th17 cells, which produce interleukin-17, have been shown to play a role in the acute phase of myocarditis. The microRNA mmu-miR-721, which is synthesized by Th17 cells, was present in the blood of mice with acute autoimmune or viral myocarditis. Hsa-miR-Chr8:96, the human homologue was identified in patients with myocarditis, and it showed high sensitivity and specificity for the diagnosis of myocarditis. Another microRNA, miR-4763-3p, was found in adult fulminant myocarditis [148]. Moreover, miR-208 was elevated in acute viral myocarditis in pediatric patients, and miR-208b levels correlated with recovery of systolic left ventricular function in the chronic stage [149].

4. Therapy

4.1. Immunosuppressive agents

Immunosuppressive therapy has been used in the treatment of myocarditis. Corticosteroids, cyclosporine, and azathioprine have been tested for protection against myocarditis [150]. These drugs are frequently used in combination, but it is necessary to evaluate their benefits for the subtypes of myocarditis in appropriate clinical comparative studies.

High doses of immunoglobulin had a beneficial effect on acute myocarditis in small case studies [151], but a randomized controlled study on patients with dilated cardiomyopathy did not support this observation [152].

4.2. Anti-viral agents

Anti-viral drugs were studied in patients with viral myocarditis in whom the etiology was specifically determined [9,25,150]. These studies were small, but the benefit of anti-viral treatment seems to be consistent regarding a decreased viral load, ejection fraction, and survival. Immunosuppressive and/or immunomodulatory treatment, such as corticosteroids and/or immunoglobulin, has been included in protocols [153]. The latter shows the involvement of immune-mediated damage, in addition to direct viral cytotoxic effects, in the development of viral myocarditis.

Interferon-α was reported to be beneficial in dilated cardiomyopathy associated with enteroviruses hemodynamically. Interferon-β improved the ejection fraction and viral load in acute viral myocarditis [153], but there was no benefit observed in a cohort of patients treated at the stage of dilated cardiomyopathy [154].

4.3. Therapeutic challenges

In our model of viral myocarditis and cardiomyopathies, immunosuppressive agents, such as prednisolone and cyclosporine, enhanced viral replication and aggravated the course of acute myocarditis. Anti-viral agents, interferon-α and ribavirin, inhibited viral replication and improved myocarditis [1]. FLCs, IL-12, a β-adrenergic blocker, carvedilol, and pycnogenol had anti-viral and anti-inflammatory effects, and they were beneficial for acute myocarditis. Mast-cell-stabilizing agents, inhibitors of NF-κB and the renin–angiotensin–aldosterone system, fingolimod, and calcium channel blockers prevented myocarditis and showed potential in the treatment of viral myocarditis [1] (Figure 5); however, these agents did not show anti-viral effects, suggesting that their beneficial effects are due to anti-inflammatory or immunomodulating effects.

Ongoing clinical trials are assessing the role of high-dose methylprednisolone in patients with acute myocarditis complicated by heart failure or cardiogenic shock (the Myocarditis Therapy with Steroids (MYTHS) trial); the role of anakinra, an IL-1 receptor antagonist (Anakinra versus Placebo for the Treatment of Acute Myocarditis (ARAMIS)), excluding patients with a hemodynamically unstable condition; and the role of abatacept (a CTLA-4-directed fragment aimed at blocking T-cell co-stimulation by CD80 or CD86) in the treatment of immune-checkpoint-inhibitor-induced myocarditis (Abatacept for the Treatment of Immune-Checkpoint Inhibitors Induced Myocarditis (ACHLYS)) [155].

The growing knowledge on the immunopathogenesis of myocarditis will contribute to the development of effective diagnostic, prognostic, and therapeutic strategies. Soluble antibodies against coxsackievirus – adenovirus receptor extracellular domains, anti-IL-17 antibodies, cell-based therapies, and the modulation of the gut microbiome are potential preventive and therapeutic strategies for myocarditis [3]. Future directions should focus on a proper diagnostic tool, examining not only the etiological aspect but also the specific stage of the evolution of the immune/inflammatory processes.

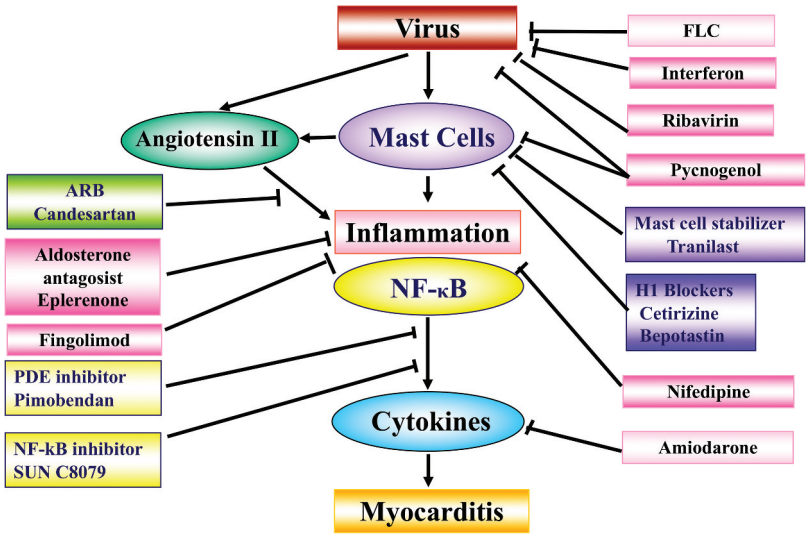

Figure 5. Anti-inflammatory therapy for viral myocarditis. Anti-viral drugs, mast-cell-stabilizing agents, inhibitors of nuclear factor (NF)-κB, the renin–angiotensin–aldosterone system, interleukin (IL)-10, and IL-12, fingolimod, carvedilol, nifedipine, amiodarone, pycnogenol, and immunoglobulin-free light chains (FLCs) prevented viral myocarditis in experimental murine models of viral myocarditis and showed potential in the treatment of myocarditis [1].

5. Conclusions

The causes of autoimmune myocarditis are heterogeneous. Since undetected infectious agents might be responsible, clarifying the etiologies is important. Autoimmune myocarditis is a serious complication of treatments with immune checkpoint inhibitors. Early diagnosis is important for the treatment of myocarditis, and novel biomarkers, including inflammatory biomarkers and the markers of myocardial injury, need to be taken into account for its diagnosis in the early stages. Since there is no specific treatment for autoimmune myocarditis, future directions of treatment should focus on a proper diagnostic tool, examining not only the etiological aspect but also the specific stage of the evolution of the immune and inflammatory processes.

6. Expert opinion

Autoimmune myocarditis may develop alone without any association with the involvement of other organs, but it might be a response to undetected infectious agents. Myocarditis is dependent on the genetics of the host, as seen in other autoimmune diseases. H2 locus, the major histocompatibility complex (MHC) of the mouse, is an important determinant of the severity of disease induced by cardiac myosin or coxsackievirus B3 infection, but multiple non-MHC immunoregulatory genes are critical in determining susceptibility.

Viral infection may play an important role in the pathogenesis of autoimmune myocarditis. SARS-CoV-2 infection stimulates the immune system and has been shown to be linked to autoimmune diseases. Although the pathogenetic mechanism is unknown, SARS-CoV-2 infection may stimulate the production of multiple autoantibodies, which may result in autoimmune diseases.

Disruption of an inhibitory receptor, the programmed cell death 1 (PD-1) receptor, led to lethal myocarditis and heart failure in PD-1-deficient mice. Although the efficacy of immune checkpoint inhibitors (ICIs) has been shown against cancer, ICI therapies can cause immune-related adverse events, and they lead to autoimmune myocarditis. A recent study has shown that α-myosin is an important autoantigen in ICI-myocarditis and clarified the critical role of cytotoxic CD8+ T cells in the pathogenesis of ICI toxicity.

Myocarditis was documented in individuals after they received COVID-19 vaccines, and most of them developed symptoms following the second dose. A recent study of young adults and adolescents with myocarditis showed increased circulating levels of full-length spike protein unbounded by antibodies. These findings are novel, but the pathogenetic role of the spike protein in mRNA vaccine myocarditis remains to be clarified.

Endomyocardial biopsy is invasive, there may be a sampling bias or error, and it may not be the gold standard for the diagnosis of myocarditis. CMR imaging is helpful in evaluating autoimmune myocarditis. Recently identified biomarkers of inflammation and myocyte injury are promising for the diagnosis of myocarditis when measured simultaneously.

Several subsets of T lymphocytes, including CD4+, CD8+, Treg cells, and TH17, have been implicated in myocarditis. TH17 cells were shown to promote the development of dilated cardiomyopathy from myocarditis, but Treg cells may protect against inflammation and are reduced in myocarditis.

Increased circulating FLCs have been proposed to be biomarkers of B cell activity in many inflammatory and autoimmune conditions, and FLCs have been correlated with disease activity in inflammatory and autoimmune diseases, suggesting their role as potential therapeutic targets in such conditions. Recent studies demonstrated that FLC λ and the κ/λ ratio showed good diagnostic potential for the identification of myocarditis and that the FLC κ/λ ratio could also be used as an independent prognostic factor for overall survival.

Immunosuppressive therapy has been used in the treatment of myocarditis. Corticosteroids, cyclosporine, and azathioprine have been tested for protection against myocarditis. High doses of immunoglobulin had a beneficial effect on acute myocarditis in small case studies, but a randomized controlled study on patients with dilated cardiomyopathy did not support this observation. Future treatments should focus on the appropriate diagnosis of the etiologic agent, as well as on the specific stage of the evolution of immune and inflammatory processes.

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