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Immunopathogenesis and immunomodulatory therapy for myocarditis

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Myocarditis is an inflammatory cardiac disease characterized by the destruction of myocardial cells, infiltration of interstitial inflammatory cells, and fibrosis, and is becoming a major public health concern. The aetiology of myocarditis continues to broaden as new pathogens and drugs emerge. The relationship between immune checkpoint inhibitors, severe acute respiratory syndrome coronavirus 2, vaccines against coronavirus disease-2019, and myocarditis has attracted increased attention. Immunopathological processes play an important role in the different phases of myocarditis, affecting disease occurrence, development, and prognosis. Excessive immune activation can induce severe myocardial injury and lead to fulminant myocarditis, whereas chronic inflammation can lead to cardiac remodelling and inflammatory dilated cardiomyopathy. The use of immunosuppressive treatments, particularly cytotoxic agents, for myocarditis, remains controversial. While reasonable and effective immunomodulatory therapy is the general trend. This review focuses on the current understanding of the aetiology and immunopathogenesis of myocarditis and offers new perspectives on immunomodulatory therapies.

myocarditis, etiology, pathogen, immunopathogenesis, immunomodulatory

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Introduction

Myocarditis is an inflammatory cardiac disease characterized by the destruction of myocardial cells, interstitial inflammatory cell infiltration, and fibrosis (Caforio et al., 2013). The onset of myocarditis can be slow or rapid (Ammirati et al., 2021). Mild cases are usually limited and may have no obvious symptoms, whereas severe cases may be associated with acute myocarditis (AM) or fulminant myocarditis (FM) (Cooper, 2009). Patients with acute severe myocarditis frequently experience refractory arrhythmias, cardiogenic shock, and sudden cardiac death (Frustaci et al., 2021; Sagar et al., 2012). Mechanical circulatory support (MCS) (Sieweke et al., 2020) or heart transplantation (de Roos, 2022) may be required.

The mechanism underlying myocarditis remains unclear. Up to 20% of sudden deaths in young people are caused by myocarditis (Feldman and McNamara, 2000), yet this condition remains an underestimated cause of sudden death in children and teenagers (Caforio et al., 2013). The actual prevalence of myocarditis is unclear, as it is often difficult to diagnose (Blanco-Domínguez et al., 2021). The estimated number of myocarditis cases exceeded three million in 2017, representing an increase of 59.6% over the number of cases reported in 1990, indicating that myocarditis is becoming a developing disease that spans all ages and a global public health concern (Law et al., 2021; Wang et al., 2021c).

The progression of myocarditis is usually associated with immune dysfunction (Javadi and Sahebkar, 2017). In most cases, pathogen- or damage-associated molecular patterns

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(PAMPs or DAMPs) are triggered by external factors, including viruses and other pathogens, resulting in myocardial injury that leads to overactivation of the immune response, especially the innate immunity (Tschöpe et al., 2021). Exposure to or release of myocardial-specific autoantigens also stimulates innate and acquired immune responses ranging from mild transient responses to overwhelming FM (Tajiri et al., 2021; Wu et al., 2021c). Several aetiologies are likely involved in a common immune-mediated pathogenic process that may lead to chronic inflammation and tissue damage, resulting in myocardial remodelling (De Luca et al., 2018). However, the prognosis of myocarditis depends on many factors (Tajiri et al., 2021). In particular, FM remains a challenging clinical issue that often has devastating consequences (Hang et al., 2020; Montero et al., 2022).

Due to the recent great progresses in myocarditis research, this review mainly discusses the history, trends, aetiology, immunopathogenesis, and immunomodulatory therapies for myocarditis. We also focus on the immunopathogenesis of immune checkpoint inhibitor (ICI)-related myocarditis, novel coronaviruses such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and coronavirus disease 2019 (COVID-19) vaccine-related myocarditis. This review is mainly directed at clinically significant acute and fulminant myocarditis. We aim to describe a new immunological basis for the pathogenesis and treatment of myocarditis, to propose a more reasonable and effective immunomodulatory therapy, and to inform future studies that will lead to better understanding, diagnosis, and treatment of myocarditis.

History and trends of myocarditis

Myocarditis, an ancient disease, has been explored for hundreds of years (Figure 1). The recognition of myocarditis as a disease entity began with the introduction of the term by Sobernheim in 1837 (Weinstein and Fenoglio, 1987). Romberg described myocardial infiltration associated with scarlet fever and typhus in 1891, and then Fiedler first reported isolated idiopathic interstitial myocarditis in 1897 (Weinstein and Fenoglio, 1987). With the continuous correction and change of cognition in different diseases, the study of myocarditis has been greatly developed in the 20th century. In the 1950s, many types of myocarditis, including viral myocarditis, have been found by researchers through autopsy (Blankenhorn and Gall, 1956). After the 1970s, with the application of endomyocardial biopsy, the understanding of the pathological subtypes of myocarditis has been suggested to a great extent (Lie, 1988). At the same time, the relationship between myocarditis and dilated cardiomyopathy was gradually concerned (Kawai et al., 1987). As a result, the Dallas criteria for clinical diagnosis of myocarditis was proposed in 1987 (Aretz, 1987). In addition, the use of cardiac magnetic resonance and the formulation of the Lake Louise Criteria are also helpful to the diagnosis of myocarditis (Friedrich et al., 2009). Since the 1990s, immunosuppressive therapy, MCS and immunomodulatory therapy have been successively tried to treat patients with acute or chronic myocarditis (Basso, 2022). However, newer forms of myocarditis are constantly emerging and becoming new concerns in the 21st century (Basso, 2022). In general, the future trend of myocarditis will be more diversified and challenging, requiring more support in diagnosis and treatment.

Aetiology of myocarditis

Causes of myocarditis

The aetiology of myocarditis is heterogeneous and includes infectious and non-infectious causes (Figure 2). In most cases, myocarditis is triggered by external factors such as pathogens (Tschöpe et al., 2021). Pathogenic microorganisms associated with infectious myocarditis include viruses, bacteria, fungi, spirochetes, rickettsia, and parasites (Pollack et al., 2015; Tschöpe et al., 2021). Viral myocarditis (VMC) is the most common form of myocarditis (Pollack et al., 2015). Common viruses associated with myocarditis include cardiotropic viruses such as enteroviruses and adenoviruses, vasculotropic viruses such as parvovirus B19, and lymphotropic viruses such as human herpesvirus 6 (Tajiri et al., 2021). Metagenomic sequencing and *in-situ* hybridization have identified diverse viruses, including myocarditis-related pathogens. With the application of metagenomic sequencing and in situ hybridization, diverse types of viruses have been discovered, which has significantly advanced the identification of myocarditis-related pathogens (Andréoletti et al., 2009). A shift has been observed in viral prevalence, from major adenoviruses and enteroviruses to parvovirus B19 and human herpesvirus (Law et al., 2021).

Some viruses that do not directly infect cardiomyocytes can indirectly cause cardiac injury and negative inotropic effects by triggering an immune response or cytokine storm (Jensen and Marchant, 2016). These include Zika virus (Scatularo et al., 2022), Dengue virus (Yacoub et al., 2014), and Ebola virus (Chertow et al., 2017). In addition, coronaviruses, including Middle Eastern respiratory syndrome coronavirus, SARS-CoV, and SARS-CoV-2 can cause cardiac injury and myocarditis via angiotensin-converting enzyme 2 (ACE2) tropism, cytokine-mediated cardiotoxicity, or by triggering autoimmune responses to cardiac components (Tschöpe et al., 2021). These coronaviruses can also indirectly trigger myocardial inflammation in a manner similar to influenza A and B viruses (Van Linthout et al., 2020). Bacteria can also cause myocarditis (Wang et al., 2021b). *Streptococcus* spp., *Corynebacterium diphtheriae*,

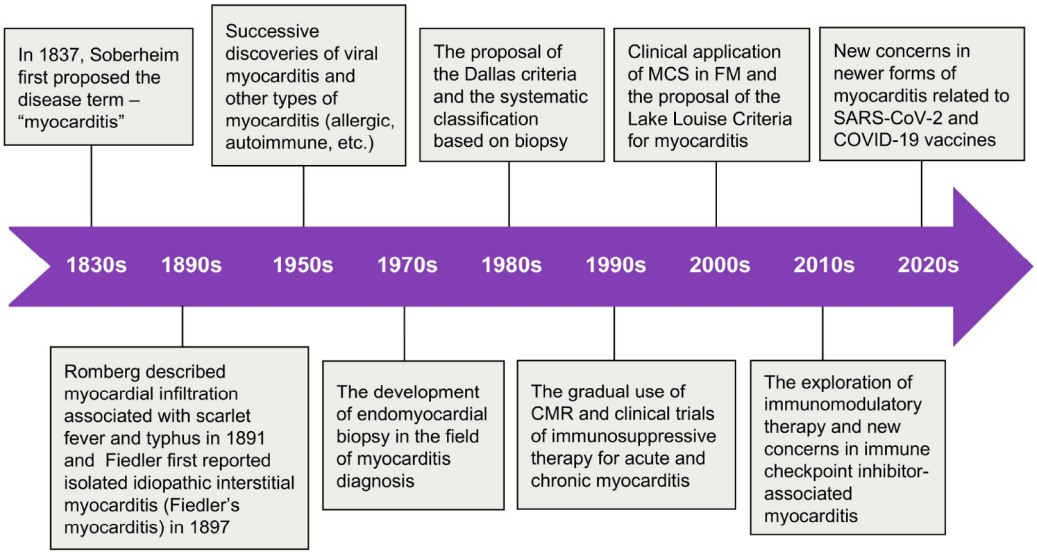

Figure 1 Timeline of myocarditis. CMR, cardiac magnetic resonance.

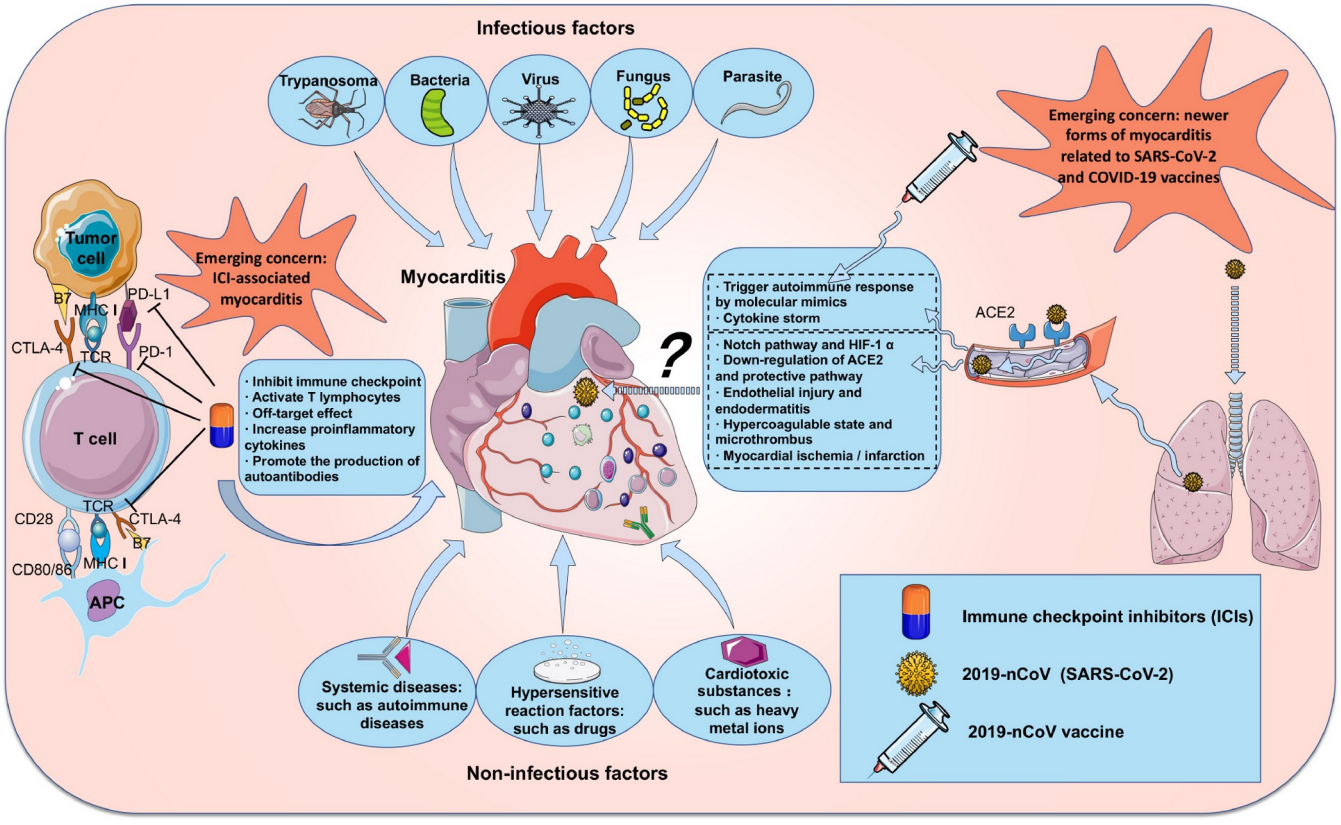

Figure 2 Illustration of the aetiology of myocarditis and two emerging concerns. Myocarditis has infectious and non-infectious causes. Infectious causes include viruses, bacteria, fungi, and parasites. Non-infectious factors are divided into systemic diseases, hypersensitive reactions, and cardiotoxic substances. Viral infection is the most common cause of myocarditis. The association between ICIs, SARS-CoV-2/COVID-19 vaccine, and myocarditis is an emerging concern. ICIs can cause myocarditis by blocking immune checkpoints (CTLA-4, PD-1, and PD-L1) that control T cell activity, leading to abnormal T cell activation or other effects. The SARS-CoV-2/COVID-19 vaccine can induce myocardial inflammation and injury by facilitating the binding of spike proteins to angiotensin-converting enzyme 2 receptors, leading to cytokine storms. CTLA-4, cytotoxic T lymphocyte-associated protein 4; PD-1, programmed cell death protein-1; PD-L1, and programmed death-ligand 1.

and mycobacterium conjugates are the leading causes of myocarditis in developing countries (Chanh et al., 2022; Sagar et al., 2012). *Porphyromonas gingivalis*, a common oral pathogen, induces myocarditis in rats (Peron et al.,

2022). Additionally, *Borrelia burgdorferi*—a bacterium that causes Lyme disease—and *Trypanosoma cruzi*—a protozoan that causes Chagas disease—causes myocarditis in specific geographical areas (Yeung et al., 2021).

Non-infectious factors associated with myocarditis include systemic diseases (such as autoimmune diseases), hypersensitivity, drugs, and cardiotoxic substances (Cheng et al., 2022; Kanai-Yoshizawa et al., 2013). Approximately 7.2% of patients with AM have autoimmune diseases (Ammirati et al., 2020). Myocarditis may be a part of systemic immune-mediated diseases such as sarcoidosis, systemic lupus erythematosus, systemic sclerosis, antiphospholipid syndrome, skin polymyositis, and other vasculitis syndromes (Cheng et al., 2022; Comarmond and Cacoub, 2017). Recently reported causes of myocarditis include hyperthyroidism (Wu et al., 2021a) and pheochromocytoma (Ammirati et al., 2020). Hypersensitive myocarditis is characterized by eosinophil infiltration (Brambatti et al., 2017). It is commonly associated with drugs, but can also occur in response to herbs, toxins, infections, malignant tumors, and food allergies (Brambatti et al., 2017). The commonest drugs include antipsychotics, antineoplastic-immunotherapies, and salicylates (Nguyen et al., 2022b).

Immune checkpoint inhibitor-associated myocarditis

In 2018, the Nobel Prize in Physiology and Medicine was jointly awarded to Dr. James Allison and Dr. Tusu Kubenzo for their discovery of cancer treatments involving the suppression of negative immunoregulation using ICIs (Bonaca et al., 2019; Sharma and Allison, 2015). However, the use of ICIs in oncology has raised concerns regarding immune-related adverse events (irAEs), including ICI-associated myocarditis (Moslehi et al., 2021). Commonly used ICIs include monoclonal antibodies (mAbs) that block cytotoxic T lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein-1 (PD-1), and programmed death-ligand 1 (PD-L1) (Moslehi et al., 2021). Although ICI-associated FM is a relatively rare form of irAE, it is often fatal and should attract enough attention (Moslehi et al., 2021; Veronese and Ammirati, 2019). Furthermore, myocarditis usually occurs early (most within three months) following the initiation of treatment with ICIs (Mahmood et al., 2018). However, cardiotoxicity can occur at any time during treatment and may occasionally occur even after discontinuation of ICIs due to their long-lasting effects (Patel et al., 2021).

Multiple injury mechanisms may concurrently affect cardiac function and lead to associated myocarditis (Jiménez-Alejandre et al., 2022). First, ICIs targeting the CTLA4, PD1, and PD-L1 pathways can relieve these immune checkpoints, leading to unlimited activation of cytotoxic T cells, which cause direct heart injury (Bermas and Zaha, 2021). Second, clonal and high-frequency T cell receptor sequences from tumor cells and cardiomyocytes can be confused by activated T cells. ICIs can enhance off-target effects by promoting T cell function, causing T cells to destroy cardiomyocytes that share antigens with tumor cells (Johnson et al., 2016). Third, ICIs can promote the infiltration of inflammatory molecules into myocardial tissue and the expansion and differentiation of T cells into T helper (Th) subtypes (Moslehi et al., 2021; Sury et al., 2018). Fourth, ICIs promote the production of autoantibodies, leading to autoimmune responses (Johnson et al., 2016; Sury et al., 2018). Additionally, a recent study has indicated that T cells specific for α-myosin play a vital role in ICI-associated myocarditis (Axelrod et al., 2022).

Anti-CTLA-4 mAbs can prevent CTLA-4, which is located on the T cell surface, from binding to B7 protein, which is located on the surface of antigen-presenting cells (APCs), thus reducing the threshold of T cell activation (Rikhi et al., 2021). It can also act on T-regulatory cells (Tregs) expressing CTLA-4 (Ha et al., 2019). Altered inhibitory Treg functions increase T-cell activity and disrupt Th1/Th2 cell balance in murine heart (Han et al., 2012; Moslehi et al., 2021). PD-1, located on activated T cells, helps to recruit other cardiac-infiltrating immune cells, particularly macrophages and neutrophils (Tarrio et al., 2012). Anti-PD-1/PD-L1 mAbs can inhibit PD-1 or PD-L1 strongly expressed on T- and natural killer (NK) cells during myocarditis, thus attacking the heart and significantly increasing the expression of interferon-gamma (IFN-γ), Fas ligand, pore-forming protein, and myocardial inflammation (Seko et al., 2007). Anti-PD-1 stimulating mAbs can decrease myocardial inflammation in the development of murine acute myocarditis caused by Coxsackievirus B3 (CVB3) (Seko et al., 2007). In addition, anti-CTLA-4 and anti-PD-1/PD-L1 mAbs show strong selection for infiltrating T cells and myocarditis (Rikhi et al., 2021). Specifically, CTLA-4 inhibition often leads to giant cell myocarditis, particularly $CD4^+$ T-cell infiltration. PD-1/PD-L1 inhibition leads to increased lymphocytic myocarditis, particularly $CD8^+$ T cell infiltration (Rikhi et al., 2021). A recent study through multiomics single-cell technology indicated that $CD45RA^+$ effector memory $CD8^+$ T Cells (Temra) characterized by increased expression of proinflammatory chemokines (CCL2/CCL4/CCL5) and lack of key anti-inflammatory signals played a leading role in ICI-associated myocarditis (Zhu et al., 2022).

In addition to determining the types of epitopes recognized by TCRs within the range of potential antigens and the organ and cell bias (including cytokines) of different irAEs, epigenetics will be important in explaining individual differences in ICIs users. Additionally, more studies on ICI-associated myocarditis are needed to identify specific mechanisms and therapeutic targets. The development of accurate animal models is necessary to facilitate the study of immunopathogenesis and identify additional biomarkers and bridge the gap between basic research and reality (Ji et al., 2019).

Newer forms of myocarditis related to SARS-CoV-2 and COVID-19 vaccines

SARS-CoV-2 can directly or indirectly cause cardiac injury and even multisystem inflammatory syndrome including SARS-CoV-2-related myocarditis (Barhoum et al., 2022; Li et al., 2021; Tajiri et al., 2021). Although there are a few cases of direct heart injury (Verma et al., 2022), the immune overresponse induced by SARS-CoV-2, rather than virus-mediated cytotoxicity, may be the leading cause of cardiac injury (Babapoor-Farrokhran et al., 2020; Melillo et al., 2022; Oprinca et al., 2022). There are several possible mechanisms of SARS-CoV-2-induced myocardial injury. The first involves the cytokine storm syndrome mediated by monocytes/macrophages and unbalanced Th cells (Breikaa and Lilly, 2021; Cao, 2020), which can lead to myocardial inflammation and injury (Li et al., 2021). Second, hypoxaemia and respiratory failure may aggravate cardiomyocyte injury via the Notch pathway and hypoxia-inducible factor-1 alpha (HIF-1α) (Rizzo et al., 2020). Third, myocardial inflammation is indirectly caused by downregulation of ACE2 expression and the subsequent downregulation of the ACE2/angiotensin (Ang-[1–7]/MAS protective signal pathway following the binding of the viral spike protein to ACE2 receptors on cardiomyocytes (Castiello et al., 2022; Robinson et al., 2020). Fourth, an autoimmune response may be triggered by SARS-CoV-2 spike proteins via molecular mimics of cardiac autoantigens (Heymans and Cooper, 2022). Fifth, diffuse endothelial inflammation and damage can occur in the heart due to the extensive recruitment of immune cells (Barbosa et al., 2021). Finally, a hypercoagulable state and coronary microvascular thrombosis can result in myocardial injury (Brener et al., 2022; Terpos et al., 2020).

Myocardial inflammation and viral nucleic acids have been observed during autopsies of patients who died of COVID-19 (Haslbauer et al., 2021). SARS-CoV-2 components have also been detected in cardiac macrophages and endothelial cells (Bearse et al., 2021; Wagner et al., 2021). Although individual case reports have been reported to show direct myocardial injury caused by SARS-CoV-2 (Verma et al., 2022), there is no more general clinical evidence of viruses in cardiomyocytes (Kawakami et al., 2021). In addition, typical acute lymphocytic myocarditis has not been detected in patients infected with SARS-CoV-2 (Hanson et al., 2022; Van Linthout et al., 2020). However, SARS-CoV-2-associated myocarditis may differ from typical lymphocytic VMC and may be associated with the diffuse infiltration of the monocyte/macrophage lineage (Bozkurt et al., 2021; Fox et al., 2021). The relationship between SARS-CoV-2 and typical myocarditis has not been determined due to the complexity of SARS-CoV-2 infection.

Additionally, myocarditis has been linked with COVID-19 vaccines (Cui et al., 2021; Patone et al., 2022; Perez et al., 2022). Myocarditis is a rare adverse event of the COVID-19 vaccine and appears to be more common in men and in people who have had a second vaccination (Chua et al., 2022; Heymans and Cooper, 2022). The estimated incidence of myocarditis is 2.13 per 100,000 vaccinated persons (10.69 per 100,000 in men aged 16–29 years)(Witberg et al., 2021). The risk of COVID-19 vaccine-associated myocarditis may be greater in patients with cardiovascular disease or with a history of myocarditis (Perez et al., 2022). Nevertheless, the diagnosis and treatment of this type of myocarditis are relatively simple and the clinical outcome tends to be mild in most patients (Perez et al., 2022; Witberg et al., 2021).

COVID-19 vaccines include messenger RNA (mRNA), DNA, viral vectors, inactivated viruses, and protein subunit vaccines (Soleimanpour and Yaghoubi, 2021; Tregoning et al., 2021). Of these, mRNA vaccine-related myocarditis has received greater attention (Heymans and Cooper, 2022). In some susceptible individuals, the mRNA components of the vaccine may abnormally activate the pro-inflammatory cascade as PAMPs, which play a role in the occurrence of myocarditis (Bozkurt et al., 2021). Molecular mimics of SARS-CoV-2 spike proteins and autoantigens are another possible mechanism (Heymans and Cooper, 2022). Antibodies against the SARS-CoV-2 spike may cross-react with structurally similar human protein sequences including myocardial α-myosin heavy chain (Vojdani and Kharrazian, 2020). However, these autoantibodies may be innocent bystanders of myocardial inflammation and injury or a reflection of specific immune-genetic background (Heymans and Cooper, 2022). The vaccine can also trigger pre-existing dysfunctional immune pathways in some individuals, resulting in polyclonal B cell expansion, immune complex formation, and myocardial inflammation (Bozkurt et al., 2021). Case reports have also described myocarditis associated with viral vectors (Naghashzadeh et al., 2022), inactivated viruses (Cui et al., 2021), and protein subunit vaccines (Heath et al., 2021).

Emerging concerns include ICI-associated and SARS-CoV-2/COVID-19 vaccines-associated myocarditis (Figure 2). However, VMC remains the most common type of myocarditis and has unmet clinical treatment needs. CVB3-induced myocarditis has been extensively studied. However, in practice, detecting viral nucleic acids previously implicated in myocarditis in cardiac tissue samples, even using virome sequencing, is difficult (Heidecker et al., 2020).

Immunopathogenesis of viral myocarditis

VMC pathogenesis occurs via direct or indirect damage mediated by viral infections and the host immune response (Zhao and Fu, 2018). Innate and acquired immune response pathways participate in immunopathogenesis, leading to the

occurrence and development of myocarditis (Fung et al., 2016; Tschöpe et al., 2021). Interaction between the host genetic background and the environment can also promote myocarditis (Aly et al., 2007). Immune status, sex, and age of the host determine the prognosis and outcome of VMC (Müller et al., 2021). The immune response in VCM is a double-edged sword. The response is necessary to limit or eliminate pathogens. However, a few patients with myocarditis may develop two potential extremes: excessive immune activation can rapidly induce heart injury, leading to FM (Hang et al., 2020), and chronic inflammation can lead to cardiac remodelling, inflammatory dilated cardiomyopathy (iDCM), heart failure, or death (Tschöpe et al., 2019).

Current cellular and molecular knowledge on myocarditis is mainly based on animal models (Tajiri et al., 2021). The main views indicate that typical myocarditis is a triphasic disease, that is, the transition from VMC to iDCM may occur via three phases (Figure 3) (Mason, 2003). In the first phase, viruses enter cardiomyocytes and cause myocardial damage. Innate immune cells are then activated and infiltrate to clear the pathogens (Lasrado and Reddy, 2020). The second phase is characterized by adaptive immune and autoimmune responses (Rischpler et al., 2022). However, a persistent immune response in the heart can cause chronic inflammation and myocardial remodelling, leading to iDCM, which is the third phase (Yue-Chun et al., 2021). When focusing on how myocarditis occurs, we often ignore the problem of why only a proportion of patients with viral infection have myocarditis and even recurrent and refractory VMC (Floyd et al., 2018; Takehana et al., 2003). Although the current studies cannot fully clarify the selectivity of myocarditis, the proposal of phase zero before VMC (pre-infection stage) emphasized the importance of prevention and investigation of susceptible genes and populations (Yajima and Knowlton, 2009). In fact, due to different immune statuses of the host, myocarditis can be terminated at any stage, which is why some patients have mild subclinical symptoms and good prognosis. However, the three possible pathogenic phases and two possible adverse outcomes of VMC should not be ignored by clinicians.

Phase 1: virus invasion and innate immune activation

Virus invasion and direct cardiomyocyte damage

Viruses invade the body and enter cells via endocytosis (Freiberg et al., 2014). Viral RNAs are simultaneously released from the protected icosahedral capsid composed of structural proteins and this is followed by viral replication and expansion (Sinnecker et al., 2014). Fused in sarcoma/translocated in liposarcoma (FUS/TLS), a newly discovered antiviral factor, can restrict CVB3 replication by directly inhibiting the transcription and translation of viral RNA and by regulating innate immunity (Xue et al., 2021). Eventually, the virus flows back through the blood or lymphatic organs to the heart (Corsten et al., 2012).

Once viruses reach cardiomyocytes, they can invade target cells through specific receptors or complexes. Coxsackie and adenoviruses invade cardiomyocytes through the coxsackie-adenovirus receptor (CAR) (Shi et al., 2010), decay-accelerating factor (DAF) (Martino et al., 1998), and integrin (Wu et al., 2018). In adult myocardia, CARs are mainly located at the cell-cell junction of the intercalated discs and atrioventricular node, and are physiologically involved in mediating electrical conduction (Knowlton and Lim, 2009; Lasrado and Reddy, 2020; Shi et al., 2009). Myocardial inflammation and injury can upregulate CAR and increase CVB3 infectivity in susceptible hosts (Fung et al., 2016). CAR upregulation in the heart might also induce cardiac inflammation independent of viral infection (Yuen et al., 2011). In addition to CAR, CVB3 infection also requires DAF (Selinka et al., 2004). Generally, DAF promotes the binding of CVB3 to the receptor complex, whereas CAR allows subsequent viral replication by mediating internalisation (Lasrado and Reddy, 2020). Once CVB3 enters the cell through CAR, it can activate tyrosine-protein kinase p56lck, mitogen-activated protein kinase (MAPK)1/2, and protein kinase C (PKC) signalling pathways (Liu et al., 2000; Marsland et al., 2007; Niu et al., 2017). These signalling pathways activate host cell immune responses and promote virus replication. CVB3 can also alter the cytoskeletal structure through Fyn and Abl kinases, facilitating cell invasion through tight junctions (Coyne and Bergelson, 2006).

Specific viral proteins such as protease 2A destroy cytoskeletal proteins such as the dystrophin glycan complex in cardiomyocytes and turn off the translation of c-Cbl-associated protein (CAP)-dependent transducers by cutting eukaryotic initiation factor-4G (eIF4G), leading to myocardial remodelling and dilatation (Esfandiarei and McManus, 2008; Goetzke et al., 2021; Law et al., 2021). Under normal circumstances, CAP can enhance the production of interferon regulatory factor 3 (IRF3)-dependent antiviral type I IFN by binding to the melanoma differentiation-related protein 5 to inhibit viral proliferation (Valaperti et al., 2014). In addition, cleavage of nuclear porin 98 (NUP98) by protease 2A and the subsequent destruction of the protective NRG1-ERBB4/PSEN1 signal cascade aggravates myocardial injury in CVB3-induced myocarditis (Hanson et al., 2019). CVB3 infection can also induce apoptosis by inducing the expression of proteases 2A and 3C that then activate exogenous caspase-3-mediated or caspase-8-mediated pathways and intrinsic mitochondria-mediated apoptotic pathways (Hanson et al., 2019; Yajima, 2011; Yajima and Knowlton, 2009). These observations can directly or indirectly explain the status of the virus in myocarditis. The inhibition of these harmful viral proteases might be a promising method for treating VMC (Fung et al., 2016).

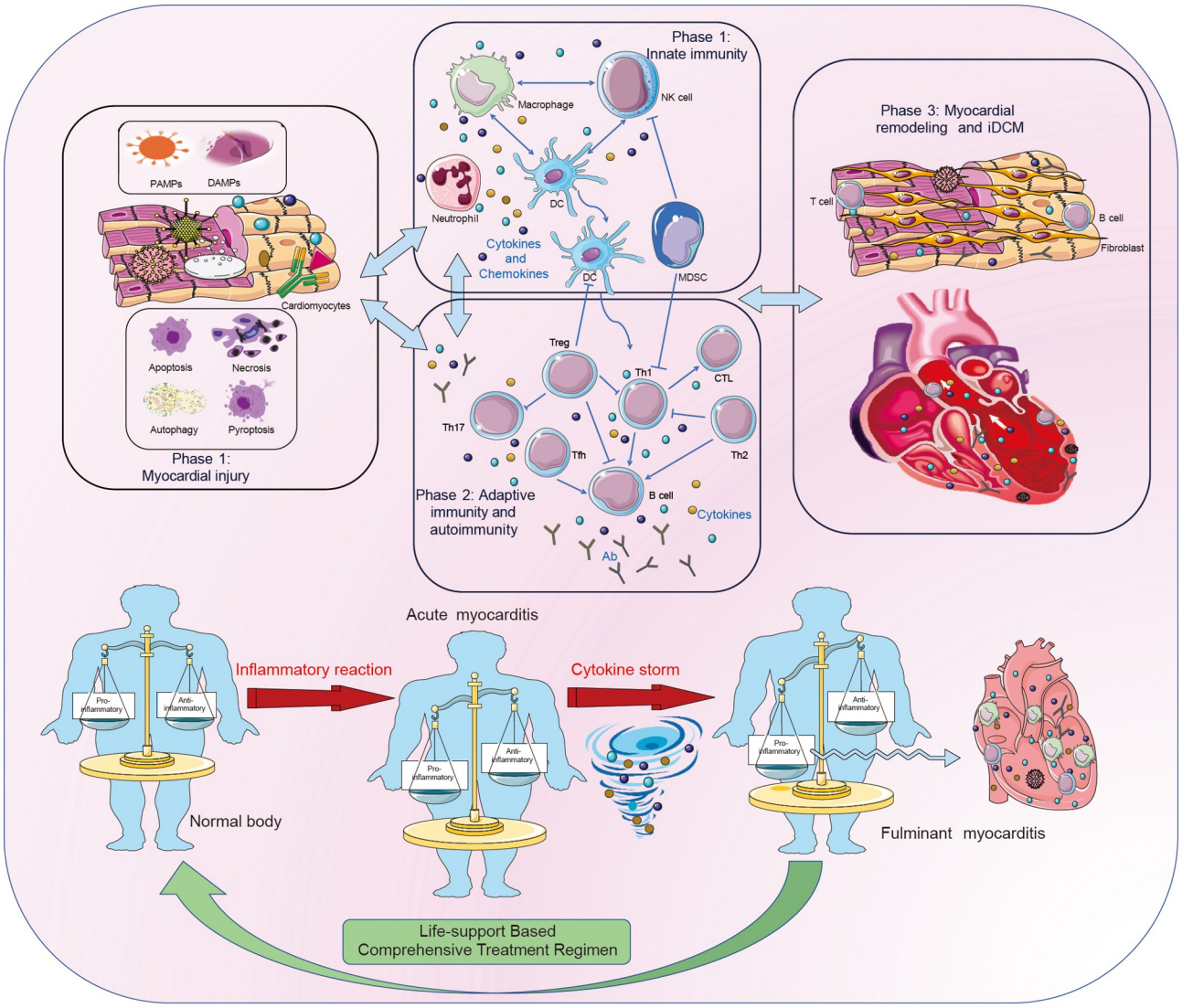

Figure 3 Illustration of immunopathogenesis and clinical outcomes of myocarditis. Myocarditis is a triphasic disease. Phase 1, viruses and other pathogenic factors cause damage (Yang et al., 2022) (apoptosis, necrosis, autophagy, or pyroptosis) to cardiomyocytes without the involvement of the host immune system. PAMPs or DAMPs bind to the TLRs of innate immune cells and activate innate immune responses. Phase 2, acquired immunity and autoimmune responses promote the deterioration of myocarditis. The activation of the immune system causes the pro-inflammatory response to slightly exceed the anti-inflammatory response, clearing the pathogenic factors and causing myocardial inflammation. If the immune response is too strong or inappropriate, the cytokine storm can destroy the heart tissue and lead to FM. In contrast, long-term chronic inflammation and autoimmune responses can cause cardiac remodelling, leading to iDCM (phase 3). The "Life-support Based Comprehensive Treatment Regimen" can be used to treat FM by regulating unbalanced inflammation and curbing the cytokine storm. TLRs, Toll-like receptors.

Host defence-innate immunity

The innate immune system is activated once viruses bind successfully to their receptors. This is important for the clinical outcomes of myocarditis. The relationship between the pathogen and the immune system is a dynamic tug-of-war in which each side tries to suppress the other (Xue et al., 2021). Innate immune cells are activated by pattern recognition receptors (PRRs), including Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain-like receptors (NLRs) that recognize PAMPs and DAMPs released from disrupted tissues and cells, including cardiac and immune cells (Khawaja and Bromage, 2021). Activated immune cells release cytokines, including chemokines, interferons, and alarmins (Lasrado and Reddy, 2020). The upregulation of proinflammatory mediators has two important short-term consequences (Mann, 2001; Medzhitov and Janeway, 2000). First, they increase the expression of cell adhesion molecules and chemokines, subsequently attracting neutrophils, macrophages, and NK cells to clean up the virus from the host cells. Second, the expression of nitric oxide synthase is upregulated. This, in turn, increases the production of nitric oxide, which is directly toxic to viral replication. Importantly, alarmins S100A8 and S100A9, which are released by neutrophils, monocytes, and myeloid-

derived suppressor cells (MDSCs), can induce oxidative stress, stimulate cytokine release, and activate macrophages, inducing an inflammatory storm in myocarditis (Khawaja and Bromage, 2021; Müller et al., 2017; Tschöpe et al., 2021).

TLRs activate signalling pathways that eventually lead to the translocation of transcription factors, mainly nuclear factor-kappa B (NF-κB), which expand the production of cytokines and induce IFN release (Kawai and Akira, 2007). Activation of TLR signalling depends on nucleic acid aptamers and kinases such as MyD88 and IL-1R-associated kinase (IRAK) (von Bernuth et al., 2012). In VMC models, MyD88 and IRAK are upregulated immediately following viral infection, leading to the subsequent activation of NF-κB (Boyd et al., 2006). Activation of TLR2, TLR4, and TLR5, but not TLR3, TLR7, or TLR9, leads to decreased contractility and a concerted inflammatory response via NF-κB (Boyd et al., 2006). TLRs can also directly induce endoplasmic reticulum stress as well as promote cytokine production (Zhang et al., 2017a). Notably, *in vitro* CVB3 infection and inflammatory factor stimulation can increase TLR7 and TLR8 expression in human cardiac cells (Triantafilou et al., 2005). Satoh et al. (2003) observed higher TLR4 mRNA expression in endomyocardial biopsy samples from patients with myocarditis than in samples from controls. In addition to TLR signalling pathways, other PRRs in the heart, including cytoplasmic retinoic acid-inducible gene I-like receptors, can also mediate the antiviral effects of IFN (Harris and Coyne, 2013).

(1) Neutrophils, monocytes and macrophages. The classical pro-inflammatory response follows the activation of innate immune responses (Goetzke et al., 2021). The activation of PRRs associated with viral infection and myocardial injury will lead to the activation and recruitment of neutrophils, monocytes and macrophages, which are mainly derived from the common myeloid progenitor in bone marrow and are essential constituents of the innate immune system (Khawaja and Bromage, 2021; Nourshargh and Alon, 2014). Neutrophils can recognize CVB3 mainly through TLR-8 and recruit chemokine to the heart in the early stage of VMC (Xu et al., 2018). Although the increase of neutrophils in the heart can reduce the ability of virus replication during acute VMC (Fairweather et al., 2005), neutrophil activity seems to be related to host tissue destruction and indicates the severity of myocarditis (Afanasyeva et al., 2004; Bartlett et al., 2004). In addition, the contribution of neutrophil extracellular traps played a considerable role in VMC (Fairweather et al., 2005). Neutrophil infiltration during the early stage, and sequential monocytes/macrophages may be the most important effector cells and pro-inflammatory cytokine producers in myocardial tissue (Rikhi et al., 2021).

Next, monocytes flow out of the bone marrow and extramedullary haematopoietic tissue following chemokine signalling and are then transported to the site of myocardial injury (Khawaja and Bromage, 2021). In fact, the clustering and function of monocytes/macrophages are extremely complex, which are the key effector cells and challenging research direction in myocarditis (Nahrendorf and Swirski, 2013). Classical pro-inflammatory monocytes ($CD14^{hi}CD16^{-}$ in humans and $Ly6C^{hi}$ in mice) are transported in a C-C chemokine receptor 2 (CCR2)-dependent manner (Bajpai et al., 2019). At the site of injury, they amplify inflammation by expressing cytokines and differentiating into macrophages (Khawaja and Bromage, 2021). Non-classical alternative monocytes ($CD14^{+}CD16^{+}/Ly6C^{low}$) with patrolling phenotype may be helpful for immune surveillance and M2 polarization of macrophages (Khawaja and Bromage, 2021; Wu et al., 2014).

Monocyte recruitment and migration are essential steps in the development of myocarditis. In VMC, cardiac-resident cells can recruit inflammatory cells to the infected myocardium (Yang et al., 2021). Infected cardiomyocytes can also transmit endoplasmic reticulum stress to macrophages to enhance the pro-inflammatory response and promote VMC pathogenesis (Zhang et al., 2017a). Monocyte chemoattractant protein 1 (MCP-1) and macrophage inflammatory protein-1 alpha (MIP-1α) are key chemokines secreted by cardiomyocytes that stimulate monocyte migration and play a role in VMC through CCR2 and CCR5, respectively (Goser et al., 2005). CVB3 infection can upregulate MCP-1 expression in cardiomyocytes (Shen et al., 2004). Kruppel-like factor 10 (KLF10) expression in non-hematopoietic cells (cardiomyocytes and cardiac fibroblasts) is necessary for VMC progression. It can reduce $Ly6C^{high}$ monocyte/macrophage infiltration into myocardium by blocking the MCP-1/CCR2 pathway, effectively alleviating VMC progression (Yang et al., 2021). In addition, stabilin-1, which is expressed in mouse and human myeloid cells, can promote the recruitment of monocytes to the inflammatory myocardium through the interaction between the extracellular fascia domain and fibronectin type III repeat sequence (Carai et al., 2021).

Monocyte subsets can migrate to myocardium under the action of chemokines and differentiate into macrophages of different sources and functions (Hou et al., 2019), which may indicate the different destinations of myocarditis. Cardiac macrophages are spatially and transcriptionally divided into three major subsets based on the expression of CCR2 and MHC (major histocompatibility complex)-II: $CCR2^{-}MHC\text{-}II^{low}$ and $CCR2^{-}MHC\text{-}II^{hi}$ macrophages are primarily derived from embryonic progenitors and renew through *in situ* proliferation, whereas $CCR2^{+}MHC\text{-}II^{hi}$ macrophages are derived from circulating blood monocytes and are slowly replenished by them (Hua and Song, 2019; Zaman et al., 2021). Macrophages undoubtedly play important and com-

plex roles in the occurrence and progression of VMC (Bao et al., 2019; Klingel et al., 1996). Moreover, macrophages are also involved in normal and abnormal cardiac electrical conduction (Bassat et al., 2017), which may be associated with arrhythmias in myocarditis (Wu et al., 2021b). There are only few single-cell RNA sequencing (scRNAseq) in the field of myocarditis research to subdivide macrophages (Hua et al., 2020; Lasrado et al., 2022). According to the results of scRNAseq in A/J mice with VMC, M2 phenotype macrophages, T lymphocytes and fibroblasts were the main types of enriched cells in the heart (Lasrado et al., 2022). *Ccl24* was the major transcript upregulated by most macrophages and might be necessary to recruit monocytes or facilitate their conversion to M2 cells, which was critical to repair damaged cardiac tissue or participate in cardiac fibrosis (Lasrado et al., 2022). scRNAseq of experimental autoimmune myocarditis (EAM) mice also showed that macrophages constituted the main immune cell group in all disease phases (>60%) (Hua et al., 2020). In addition, it's a major trend in the future to rename macrophages according to the function of macrophages in different parts (Nahrendorf and Swirski, 2016). More high-quality scRNAseq will help us to objectively understand the true state of immune cells in myocarditis.

(2) Natural killer cells. Some NK cells produce granzymes and perforins, which are cytotoxic to infected cells. In contrast, others promote the infiltration of immune cells by producing cytokines and chemokines such as TNF-α and MIP-1α (Müller et al., 2021). In VMC mice, the signal mediated by activated NKG2D receptors in NK cells effectively removed CVB3 from the heart and prevent the progression of myocarditis to iDCM (Tschöpe et al., 2021). The absence of forkhead box protein O3 (FoxO3) can lead to an accumulation of activated NK cells in the heart, characterized by increased miR-155-dependent IFN-γ expression and differentiation into effector NK cells and resulting in early virus elimination and reduction of myocardial inflammation (Loebel et al., 2018). During VMC, cardiomyocytes express CXCL10 following stimulation by IFN-γ. Early upregulation of CXCL10 can result in the recruitment of NK cells through chemical attraction and lead to inhibition of virus replication (Yuan et al., 2009). Adiponectin can promote VMC by inhibiting the TLR-dependent innate immune response, downregulating anti-inflammatory M2 macrophage polarisation, and reducing the number and activity of NK cells (Jenke et al., 2014).

(3) Dendritic cells. Dendritic cells (DCs) patrol various tissues and play a key role in initiating antiviral T cell responses (Yang et al., 2021). DCs are also the most potent antigen-presenting cells and participate in a tightly regulated multistep events involved in the induction of the immune response (Hasegawa et al., 2005). After viruses infect the myocardium, DCs gather in the heart by binding to CCR2, consistent with monocyte/macrophage infiltration. The resident DC subgroups in the heart are mainly $CD103^+$ and $CD11b^+$, which differentially rely on local proliferation and precursor recruitment to maintain their tissue residency (Clemente-Casares et al., 2017). Following the phagocytosis of dead and damaged cardiomyocytes, DCs migrate to regional lymph nodes and the spleen, present antigens to immature B and T cells, and initiate an adaptive immune response (Clemente-Casares et al., 2017). After the activation triggered by IL-1R, DCs are prerequisites for the induction of autoreactive $CD4^+$ T cells (Eriksson et al., 2003) and antigen-specific $CD8^+$ T cells (Clemente-Casares et al., 2017). The non-structural extracellular matrix glycoprotein Tenascin-C activated DCs to produce pathogenic autoreactive T cells, which were essential in connecting innate immunity with acquired immunity (Tajiri et al., 2021). Cardiac DCs have specific life cycle and properties different from other tissues, especially partly dependent on CCR2 (Clemente-Casares et al., 2017). Actually, we need to revisit the role of $CCR2^+$ monocytes versus $CCR2^+$ DCs, which will contribute to our comprehensive understanding of the dynamics in myocarditis.

(4) Myeloid-derived suppressor cells. MDSCs can inhibit both NK cells and T cells, worsening the progression of myocarditis. Aggregation and migration of MDSCs are mainly regulated by the S100A8/9 dimer. S100A8/9 induces an autocrine feedback loop in MDSCs that cancels the maturation of myeloid progenitor cells and leads to the accumulation of MDSCs (Müller et al., 2021). Moreover, interaction between MDSCs and NK cells determines VMC prognosis. Müller et al. (2021) observed that the destruction of NK cell function by MDSCs promotes the occurrence of chronic CVB3 myocarditis in A.BY/SNJ mice. When MDSCs are exhausted, attraction of pathogenic immune cells to the heart through pro-inflammatory cytokine-dependent NK cells is suppressed, resulting in reduced inflammation.

Fulminant myocarditis and cytokine storm

FM is characterized by rapid occurrence of severe myocardial inflammatory damage, which is the most severe form of AM (Huang et al., 2021). FM is sporadic, global, and not rare (Sharma et al., 2019). The small amount of epidemiological data available on FM provides a rough estimate of the FM incidence of approximately 1.0–2.0 per 1,000,000 people per year (Karjalainen and Heikkilä, 1999; Saji et al., 2012). The lack of accurate and extensive epidemiological data on FM reflects the potential misdiagnosis of this disease. FM can result in severe left ventricular systolic dysfunction, rapid clinical progression, and high mortality (Sharma et al., 2019). Clinically, most patients have obvious prodromal symptoms of viral infection and severe haemodynamic compromise (Cooper, 2017). Pathologically, almost all cases show active inflammatory infiltration of lympho-

cytes and macrophages accompanied by cardiomyocyte degeneration and necrosis (Cooper, 2017). Although a previous single-center study indicated that 15 patients with FM had better long-term prognosis compared with 132 patients with non-fulminant myocarditis (NFM) (McCarthy et al., 2000), the results were considered counterintuitive and have recently been challenged due to the relatively small number of patients with biopsy-proven myocarditis who were included in the study (Ammirati et al., 2017; Ammirati et al., 2019). A multicentre international cohort study concluded that these patients had much higher 60-day or long-term cardiac mortality and heart transplantation rates compared with patients with NFM (Ammirati et al., 2019). FM does not usually respond well to conventional vasoactive drugs such as norepinephrine and vasopressin nor to standard heart failure or cardiogenic shock treatments (Hang et al., 2020; Khairy and Infante-Rivard, 2000). Basic and clinical studies have suggested that FM may require both temporary MCS and immunomodulatory therapy (Li et al., 2019; Nie et al., 2021; Wang et al., 2022; Zhou et al., 2022).

A balanced innate and adaptive immune system is key to an effective antiviral response (Breikaa and Lilly, 2021). Our research and clinical observations showed that in patients with FM, myocardial contraction was significantly inhibited while myocardial oedema, severe inflammatory cell infiltration, and levels of pro-inflammatory cytokines in plasma increased significantly. This indicates the excessive immune activation (particularly innate immunity) and cytokine storm, which is not only the core of cardiac damage and dysfunction but also the main cause of death (Gupta et al., 2020; Hang et al., 2020; Li et al., 2019; Wang et al., 2022). To make matters worse, the body cannot effectively regulate the entire inflammation process with cytokine storm as the core, leading to systemic inflammation and catastrophic damage to surrounding tissue (Edin and Zeldin, 2019; Hang et al., 2020; Wang et al., 2022). The cytokine storm can affect myocardial contraction and cardiac electrical conduction directly, leading to cardiogenic shock and malignant arrhythmia (Gupta et al., 2020). It may also cause large-area myocardial oedema, necrosis, and a hypodynamic ventricular wall (Hang et al., 2020; Wang and Hui, 2022). The fundamental reason for the cytokine storm may lie in the imbalanced regulation of pro-inflammatory and anti-inflammatory responses. The maladjusted immune response results in a positive feedback loop between the innate immune system, adaptive immune system, non-immune cells such as endothelial cells and fibroblasts, and cytokines, leading to excessive release of cytokines (Rouse and Sehrawat, 2010; Tschöpe et al., 2021). Due to patient heterogeneity, deviation in understanding the characteristics and pathophysiology, and difficult randomized controlled trials (RCTs), the treatment of FM is still unmet and challenging. The hypothesis of cytokine storm in FM patients and the corresponding "life-support based comprehensive treatment regimen" should facilitate our understanding of the pathogenesis (Li et al., 2019; Veronese et al., 2021; Zhang et al., 2019; Zhou et al., 2021).

Phase 2: acquired immunity and autoimmune response

Host defence-acquired immunity

The host's adaptive immune response can be activated after phase 1, resulting in the production and infiltration of cytotoxic T lymphocytes (CTLs) into the heart where they directly attack viruses and virus-infected cells (Mason, 2003). T cell activation can also lead to B cell activation and production of specific antibodies that neutralize antigens (Hua and Song, 2019). Cell infiltration during acquired immunity can have two distinct effects: removal of virus-infected cardiomyocytes, which is beneficial, and secondary cardiomyocyte injury or necrosis, which is harmful and can lead to myocardial fibrosis and remodelling (Khawaja and Bromage, 2021; Sagar et al., 2012).

(1) $CD4^+$ T cells: Th1/Th2. The $CD4^+$ T cell classification model proposed by Mosman and Coffman suggests that different Th cell types play different roles in myocarditis (Yang et al., 2011). Abnormal differentiation of $CD4^+$ T cells plays a vital role in VMC progression and is associated with autoantigen presentation by type 2 DCs and the Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) and NF-κB signal transduction pathways (Van der Borght et al., 2018; Yue-Chun et al., 2021). The overactivated immune response mediated by Th cells is also an important cause of cardiomyocyte injury in VMC (Chen et al., 2021). IFN-γ and IL-12 can induce the differentiation of Th1 cells, which is characterized by the production of more IFN-γ (Yang et al., 2011). IL-12 plays a significant proinflammatory role by activating STAT4, which mediates Th1 cell responses (Afanasyeva et al., 2001). In contrast, the IFN-γ produced by Th1 cells, mediated by IL-12, can play a protective role in VMC. The disease-limiting effect of IFN-γ may be explained by its ability to activate macrophages that kill intracellular viruses and control the expansion of activated T lymphocytes (Barin et al., 2010; Sonderegger et al., 2006). Therefore, the IL-12/IFN-γ axis may be a double-edged sword in the development of AM. Although IL-12 mediates the disease by inducing and expanding Th1 cells, IFN-γ produced by these cells limits disease progression (Eriksson et al., 2001).

Th2 cells defend against extracellular pathogens and help B cells produce antibodies (Cen et al., 2021). Notably, Th2 cells can alleviate VMC by secreting IL-4, IL-5, IL-10, and IL-13. However, they can also promote iDCM progression by stimulating cardiac remodelling (Caforio et al., 2002; Maisch, 2019). The Th1/Th2 cell balance is crucial for controlling the severity of myocarditis. The hepatocyte

growth factor reduces the severity of myocarditis by inhibiting Th1 cytokines, increasing Th2 cytokines, and inhibiting cardiomyocyte apoptosis (Futamatsu et al., 2005). Peroxisome proliferator-activated receptor gamma (PPARγ) ligands can change the direction of the immune response by facilitating Th2 responses (Yuan et al., 2003). Pioglitazone has a beneficial effect on myocarditis as it activates PPARγ, which inhibits the expression of MIP-1α and regulates Th1/Th2 cell balance (Hasegawa et al., 2005).

(2) $CD4^+$ T cells: Th17/Treg. Th17 cells and Tregs are another interesting pro-/anti-inflammatory subset of Th cells that are essential for the progression of myocarditis. Th17 cells are characterized by IL-17 production and play a central role in the production of anti-myocardial antibodies and the development of iDCM, which also has a diagnostic value (Blanco-Domínguez et al., 2021; Zhu et al., 2021). Th17 cell differentiation requires the binding of IL-6, TGF-β, and retinoid-associated orphan nuclear receptor γt (RORgt) (Myers et al., 2016; Yang et al., 2011). CVB3 directly induces Th17 cell differentiation by inhibiting the expression of Nup98 during VMC (Long et al., 2016). IL-23 is secreted by APCs and acts on the IL-23R of Th17 cells to promote IL-17 production and maturation (Ahern et al., 2010). TGF-β, IL-6, and IL-21 induce IL-23R and activate Th17 cells via RORgt in a STAT3-dependent manner (Yang et al., 2011). Vaccines targeting IL-23 and IL-17 can inhibit the progression of myocarditis (Sonderegger et al., 2006). Increased NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) expression can promote the differentiation of $CD4^+$ T cells into Th17 cells. The IL-17 expressed by Th17 cells can in turn promote NLRP3 expression. The positive feedback regulatory mechanism existing in the early stages of CVB3 infection can lead to the progression and deterioration of myocarditis (Chen et al., 2021). Th17 cells can also affect myocarditis prognosis. The development of myocarditis into fatal heart disease depends on cardiac myosin-specific Th17 cells imprinted by symbiotic bacitracin mimics in the gut (Gil-Cruz et al., 2019).

However, IL-27 reportedly inhibits the production of IL-17 by Th17 cells stimulated with α-CD3/CD28, IL-6, and TGF-β, mainly through a STAT1-dependent mechanism (Zhu et al., 2015). CD69 reduces IL-17 production by negatively regulating the heart-specific Th17 response in EAM (Cruz-Adalia et al., 2010). Monoclonal anti-IL-17 antibodies can alleviate AM by inhibiting the proliferation of $CD19^+$ B lymphocytes and lowering the secretion of anti-adenine nucleotide translocator autoantibodies (Yuan et al., 2010). Notably, sacubitril/valsartan can inhibit Th17 differentiation and infiltration through the sGC/NF-κB/p65 signalling pathway, reducing IL-17 levels in myocardial tissue and peripheral blood, alleviating myocarditis (Liang et al., 2021) and thus helping to protect the heart during VMC.

As an important subgroup of $CD4^+$ T cells, Tregs ($CD4^+CD25^+Foxp3^+$) can express a variety of effectors and perform regulatory functions by directly inhibiting T/B cells and APCs or interacting with non-immune cells (Marchant and McManus, 2010; Muñoz-Rojas and Mathis, 2021; Pappritz et al., 2018). Shi et al. (2010) showed that Tregs reduced the level of CAR (TGF-β-CAR pathway) in the host heart through expression of Akt and TGF-β, inhibited the immune response to myocardial tissue, and protected mice from CVB3-induced myocarditis. In addition, Tregs can improve left ventricular function and cardiac matrix remodelling by regulating monocyte differentiation, increasing anti-inflammatory $Ly6C^{low}CCR2^{low}Cx3Cr1^{high}$ and decreasing pro-inflammatory $Ly6C^{high}CCR2^{high}Cx3Cr1^{low}$ monocyte subsets (Pappritz et al., 2018). M2 macrophages can relieve VMC by increasing the activity of Tregs (Marchant and McManus, 2010). In contrast, $\gamma\delta^+$ T cells can promote the acute memory response of $CD4^+IFN\text{-}\gamma^+$ cells by limiting the activity of Tregs (Huber, 2009). Cardiac myosin-induced tolerogenic DCs can alleviate myocardial inflammation in mice with EAM by inducing myosin-specific Tregs (Lee et al., 2014). Galectin-9 relieves CVB3-induced myocarditis by promoting Tregs proliferation and activating Th2 cells (Lv et al., 2011; Zhang et al., 2017b). However, Tregs can also lead to the persistence of viruses by prematurely limiting the antiviral immune response. Long-term maintenance of Tregs activation can lead to adaptive immune incompetence and deterioration of myocarditis (Xie et al., 2011).

The Th17/Tregs imbalance in inflammatory diseases is often apparent as a functional whole. TGF-β is regarded as a hub between Th17 cells and Tregs (Chen et al., 2021; Xie et al., 2011). A higher Th17/Tregs ratio in patients with myocarditis can lead to the recruitment of proinflammatory cytokines and inflammatory cells to the myocardium (Rikhi et al., 2021). Th17 cells can promote viral replication by limiting Tregs activity and perforin responses (Xie et al., 2011). Therefore, IL-37 can restrict the development of EAM by correcting the functional imbalance in Th17/Tregs (An et al., 2017). Myocarditis treatments targeting the Th17/Tregs imbalance may be more effective as Th17/Treg subsets evolve greater developmental plasticity compared with Th1/Th2 subsets (Xie et al., 2011).

(3) Follicular helper T cells. Follicular helper T cells (Tfh) are a recently described class of $CD4^+$ Th cells that are being studied due to their unique role in assisting B cells and promoting autoimmunity. Tfh can provide costimulatory signals and promote growth, differentiation, and B cell class conversion, leading to autoantibody overproduction through overexpression of specific costimulatory molecules such as inducible T cell co-stimulator and CD40L (Yang et al., 2015). IL-21 is preferentially produced by Tfh and promotes the development of Tfh cells that are involved in VMC-related inflammatory processes (Yang et al., 2017). As an important regulator of humoral immunity, IL-21 drives the

expansion and differentiation of B cells (Yang et al., 2015).

(4) $CD8^+$ T cells. $CD8^+$ T cells are another subset of T lymphocytes and are also the main immune cells of myocarditis (Lasrado et al., 2022). Antigen-specific CTLs can kill infected cells by releasing perforins and granzymes (Ahuja et al., 2007). Differentiated CTLs will lead to cytolysis and produce multiple cytokines, perforins, and granzymes (Liu et al., 2012a). CTLs also play two roles in myocarditis. They are important in the early stages of myocarditis and most likely function in virus clearance, while $CD8^+$ autoreactive T cells that infiltrate the heart during the chronic stage can cause the progression and deterioration of VMC (Bartlett et al., 2004). However, another study showed that deficiency of $CD8^+$ T cells in VMC mice led to the development of chronic myocarditis due to ineffective antiviral response and reduced INF-γ, which is independent of perforin-mediated pathways (Klingel et al., 2003). So far, the role of $CD8^+$ T cells in different stages of VMC is still controversial. We speculate that different functions and locations of CTL may have different effects on the clinical outcomes of myocarditis. Additionally, the role of non-immune cells (cardiomyocytes, cardiac fibroblasts and endothelial cells) in the heart should be given enough attention in myocarditis (Xuan et al., 2022).

Progression of myocarditis-autoimmune response

Based on studies on molecular mimicry and antibody cross-reactions in humoral immunity, VMC can result from an immune response to a virus and cardiac-specific autoimmune response (Błyszczuk, 2019; Gil-Cruz et al., 2019). The most important feature of the autoimmune response in VMC is the anti-heart autoantibody (AHA) produced by effector B cells (Zhu et al., 2021). VMC progression can result from an autoimmune response (Rose, 2000). If viral antigenic peptides are similar to myosin, or other myocardial antigens, the body can induce cardiac autoimmunity through cross-reaction, resulting in autoreactive T-cells that attack the myocardium. This process is known as molecular mimicry (Lowenstein, 2004; Massilamany et al., 2014). Injured cardiomyocytes expose or release more antigens, activating additional T cells by binding to TLRs, thus promoting a more severe immune response (Gangaplara et al., 2012; Rose, 2000). Notably, bacteriocin peptide mimics from the intestinal microbiota can mediate iDCM by activating heart-specific Th cells (Gil-Cruz et al., 2019). The autoimmune response is generally due to a common antigenic epitope on the virus and cardiac autoantigens and may contribute to the progression and chronicity of myocardial inflammation (Li et al., 2008; Maisch, 2019).

Approximately 30% of patients with myocarditis or iDCM produce high titers of specific AHA (Caforio et al., 2002). In particular, anti-cardiac myosin heavy chain autoantibodies have been identified as the most significant autoantibodies in patients with myocarditis, and are associated with the deterioration of left ventricular systolic and diastolic functions (Błyszczuk, 2019; Nussinovitch and Shoenfeld, 2013). β1-adrenergic receptor, M2 muscarinic receptor, cardiac myosin heavy chain subtype, and cardiac troponin can act as autoantigens that promote autoimmune responses following exposure and accelerate the progression of myocarditis (Tschöpe et al., 2021). Exposure to environmental microbes containing cardiac antigen-mimicking sequences that are otherwise harmless may also induce cardiac autoimmunity through molecular mimics, further illustrating the importance of autoimmune responses to the progression of myocarditis (Massilamany et al., 2011). Because of the autoimmune response, we believe that when viruses are controlled by the innate immune response, downregulating the autoimmune response derived from acquired immunity may be beneficial.

Phase 3: Myocardial remodelling and inflammatory dilated cardiomyopathy

AM can develop into a chronic condition in a few cases, regardless of the trigger (De Luca et al., 2018). Abnormal genetic background, reduced viral clearance, immune disorders, and persistent autoimmune responses may lead to chronic myocardial inflammation during VMC (Peretto et al., 2019; Xiao et al., 2022). Chronic myocarditis is characterized by the upregulation of cytokines and continuous accumulation of immune cells in the myocardium, resulting in myocardial remodelling, fibrosis, systolic dysfunction, or iDCM (Jenke et al., 2014). As previously mentioned, viruses can cause DCM by acting directly on and modifying the myocardial cytoskeleton. PCR analysis revealed that viral genomes persist in heart tissue for different periods. The presence of enteroviral RNA may indicate a worse prognosis (Lassner et al., 2014; Law et al., 2021). Persistent chronic myocarditis caused by persistent viruses in A.BY/SnJ mice has been attributed to the failure of effective DC maturation and activation, resulting in impaired antigen presentation (Rahnefeld et al., 2011). Excessive synergism and immune imbalance between Th1 and Th17 cells can also affect the transformation of AM to iDCM (Nindl et al., 2012).

Different from other cardiomyopathy, the typical histopathological features of iDCM are fiber repair and extracellular matrix remodelling, in addition to myocardial inflammation (Blyszczuk et al., 2017; Huang et al., 2023; Kallwellis-Opara et al., 2007; Zhang et al., 2022). In fact, some cardiac fibroblasts are activated in the early phase of myocarditis (Lasrado et al., 2022), which has not been studied in detail in post-infection stage. Following myocardial injury, cardiac fibroblasts can differentiate into myofibroblasts that reshape the myocardium by depositing excessive extracellular matrix, resulting in tissue stiffness, decreased

compliance, and cardiac dysfunction (Aghajanian et al., 2019). Myocardial fibrosis also plays a vital role in the development of arrhythmias, making myocarditis an important cause of sudden death (De Luca et al., 2018; Narducci et al., 2021). TGF-β signal activation is a critical step in the promotion of tissue remodelling in iDCM (Blyszczuk et al., 2017). Cardiac-infiltrating prominin-1^{+}/$CD133^{+}$ progenitor cells are a source of cardiac myofibroblasts in chronic myocarditis (Kania et al., 2009). The *in vitro* differentiation of fibroblasts depends on TGF-β-mediated SMAD protein phosphorylation (Kania et al., 2009). TGF-β activates the classical Wnt pathway by activating TAK1, inducing Wnt protein secretion and leading to the formation of pathogenic myofibroblasts (Blyszczuk et al., 2017). In addition, IL-11 and IL-11RA are specifically expressed in fibroblasts. The main transcriptional response to TGF-β exposure involves IL-11 upregulation and is necessary for its fibrogenic effect. IL-11 inhibition can prevent fibroblasts from activating a series of important fibrogenic stimuli across different organs and species (Schafer et al., 2017).

Several T and B cells also play important roles in promoting or alleviating chronic myocarditis. Cardiac myosin TLR ligands can stimulate monocytes to produce Th17-promoting cytokines (IL-6, GM-CSF, IL-17, and TGF-β) and Th17 cells that promote fibrosis (Myers et al., 2016). IL-17 participates in myocardial fibrosis through the PKCβ/Erk (1/2)/NF-κB pathway (Liu et al., 2012b). Experimental results are consistent with the theory that MMP-2/9 expression, gelatinase activity, and interstitial myocardial fibrosis are reduced in IL-17-deficient mice (Baldeviano et al., 2010). In contrast, Th22 cells inhibit myocardial fibrosis by producing cardioprotective IL-22 (Kong et al., 2012), which may be associated with reduced COL1-A1, COL3-A1, and MMP9 and elevated TIMP-1 as a myocardial protective cytokine (Guo et al., 2014). Few studies have investigated the role of B cells in the progression of myocarditis into iDCM (Tschöpe et al., 2021). One study suggested that T cell activation and B cell epitope diffusion are vital in the transition from myocarditis to iDCM in rats immunised with recombinant cardiac C-protein fragment 2 (CC2) (Matsumoto et al., 2007).

New viewpoints on immunosuppressive/immunomodulatory therapies

Immunotherapies of myocarditis focused on immunosuppression in the past few years (Cheng et al., 2021). However, there is insufficient evidence to support the routine use of single or combined immunosuppressants such as prednisone with azathioprine or cyclosporine in the treatment of acute or fulminant myocarditis (Bockstahler et al., 2020; Winter et al., 2018). The benefits of immunosuppressive therapies have not been systematically discovered and reported in patients with AM or FM. Although some studies have shown that early IS therapy against acute lymphocytic myocarditis with persistent heart failure can have immediate benefits (Weitsman et al., 2016), there is still not enough theoretical or practical basis.

The viral infection itself may not be the main concern for patients with FM (Hang et al., 2020). What is urgently needed is to inhibit the overactivated immune response and quell the cytokine storm and its adverse consequences, including myocardial oedema, cardiac dysfunction, and cardiogenic shock. Therefore, the immunomodulatory therapy using sufficient doses of glucocorticoids (GC) combined with intravenous immunoglobulin (IVIG), rather than routine immunosuppressive therapy, should be an effective and reliable choice in AM and FM patients (Ammirati et al., 2021; Li et al., 2019; Wang et al., 2019). In clinical practice, immunomodulatory therapy combined with a sufficient dose of GC and IVIG has been shown to regulate the immune system and correct early immune disorders in patients with FM, effectively reducing the mortality risk in patients with FM from more than 50% to 3.7% with the help of MCS. The efficacy of this systematic treatment has been replicated at different centers (Edin and Zeldin, 2019; Li et al., 2019; Wang and Hui, 2022).

GC has immunosuppressive and potent anti-inflammatory and anti-shock effects, and may have several beneficial effects on inflammatory regulation, improvement of cardiac metabolism and function, and patient survival (Cain and Cidlowski, 2017; Law et al., 2021). The use of GC may prevent shock, improve myocardial oedema, and calm the cytokine storm in patients with FM (Chen et al., 2013; Hu et al., 2021). Additionally, there is no evidence that GC increases viral replication or worsens myocarditis (Chen et al., 2013; Cheng et al., 2021), especially during FM (Li et al., 2019). Notably, we observed that during FM, not only did GC not promote viral replication, it improved cardiac function and reduced viral titer. The underlying mechanism may involve the inhibition of arachidonic acid metabolism in FM, whereas GC improves arachidonic acid metabolism and increases epoxyeicosatrienoic acids (Wang et al., 2021a), promoting the secretion of IFN to clear the viruses. However, the application of pan-immunosuppressive therapy in myocarditis, represented by GC with cytotoxic drugs, remains controversial (Veronese et al., 2021). Infection, gastrointestinal side effects, and uncontrolled diabetes are the main risks of concern in patients with myocarditis who are treated with GC (Pussadhamma et al., 2020). More studies are needed to determine safety, effective dosage, proper pathological type, and optimal GC administration times for myocarditis treatments. Finally, other independent adverse effects associated with long-term use of GC, such as osteoporosis, cannot be ignored during the treatment of myo-

carditis (Buckley and Humphrey, 2018).

IVIG has no obvious immunosuppressive effects but exhibits anti-inflammatory, antiviral, and immunomodulatory effects (Law et al., 2021). High-dose IVIG is beneficial for treating AM, especially FM (Huang et al., 2019; Tedeschi et al., 2002; Wang et al., 2019). In addition to routine immunosuppressive therapy, immunoadsorption and subsequent IVIG substitution are associated with greater improvement in left ventricular ejection fraction (LVEF) (Winter et al., 2018). TNF-α expression decreased in groups of patients treated with different doses of IVIG, although a double dose was more effective at improving the progress of myocarditis, potentially mediated by the regulation of the immune response (George et al., 2001). A meta-analysis showed that IVIG improved LVEF and reduced hospitalisation and mortality in patients with AM, particularly FM (Huang et al., 2019). Notably, only early persistent IVIG, rather than $F(ab')_2$ fragments, can effectively ameliorate myocarditis, which is associated with the inhibition of DC expression and IL-1β production during both early and subsequent fulminant phases (Shioji et al., 2001). IVIG is effective against different types of FM models. Moreover, in the absence of co-IM therapy with GC and IVIG, the protective effects of GC in promoting the production of nitric oxide, reducing myocardial oedema, and improving the survival of cardiomyocytes, and the beneficial effects of IVIG are significantly weakened (Hafezi-Moghadam et al., 2002).

There are encouraging results on new immunomodulatory mechanisms and therapeutic drugs (Cavalli et al., 2016). IL-1 is an apical proinflammatory mediator involved in acute and chronic inflammation (Noji, 2016). The intracellular contents released by dying cardiomyocytes during myocarditis trigger the activation of inflammasomes and the uncontrolled release of IL-1 by adjacent cells (De Luca et al., 2018). Anakinra is a recombinant form of naturally occurring IL-1Ra that specifically reduces the activity of IL-1α and IL-1β. It has been used to treat IL-1-mediated inflammatory diseases as it rapidly and safely blocks IL-1R (Abbate et al., 2020; Cavalli et al., 2017). The SAVE-MORE trial showed that anakinra treatment can prevent COVID-19 from worsening into a critical disease (van de Veerdonk et al., 2022). Preliminary clinical studies of anakinra indicate that IL-1 inhibition is effective at reducing myocardial inflammation and systolic dysfunction in AM and FM (Ammirati et al., 2021; Cavalli et al., 2016; Cavalli et al., 2021). The efficacy may be due to direct blocking of IL-1R and indirect inhibition of the production of IL-1 and IL-18, inhibiting the activation of various pro-inflammatory immune cells and calming the cytokine storm (Abbate et al., 2020; Bird, 2018). Furthermore, anakinra can weaken cyclooxygenase-2/prostaglandin E2 signal transduction by blocking IL-1R in cardiac lymphatic muscle cells, attenuating the decrease in the contractile force of these muscle cells caused by IL-1β, and inhibiting the accumulation of inflammatory mediators in the heart (Al-Kofahi et al., 2018) (Figure 4).

Immunomodulatory therapy is also suitable for newer forms of myocarditis. GC and IVIG are recommended for ICI-associated myocarditis, which can reduce the incidence of major adverse cardiovascular events (Lehmann et al., 2021; Mahmood et al., 2018). In clinical research, abatacept is a CTLA-4 fusion protein that targets CD80/86 (B7-1/B7-2) on APCs, causing global T cell anergy, and is currently under evaluation in clinical trials (NCT05195645, NCT03619876) (Wei et al., 2021). Successful treatment of ICI-associated myocarditis has been reported in some cases (Nguyen et al., 2022a; Salem et al., 2019). However, the possible complications of infection and the risk of promoting tumor growth should also be concerned in abatacept treatment (Salem et al., 2019). Immunomodulatory therapy rather than immunosuppression alone can also be used in patients with COVID-19 and COVID-19 vaccine-associated myocarditis (Gluckman et al., 2022; Mele et al., 2021; Siripanthong et al., 2020). Immunosuppression may pose a more serious clinical risk to patients with COVID-19-related myocarditis, especially in the stage of active viral replication (Siripanthong et al., 2020). Immunomodulatory therapy can reduce cytokine storm and improve cardiac function through anti-inflammatory and antioxidant stress (Okor et al., 2022). In addition, some cytokine modulators, including Toclizumab, Siltuximab, and Sarilumab, may have potential therapeutic effects on COVID-19-related myocarditis (Wang et al., 2021d).

Few clinical trials have reported conclusive results on myocarditis immunotherapies. The Myocarditis Treatment Trial (NCT00000524), a long-term clinical cohort study, showed that prednisone combined with either cyclosporine or azathioprine had no beneficial effect on the main endpoint (LVEF at 28 weeks) or on survival (Hahn et al., 1995; Mason et al., 1995). However, despite the lack of clear evidence, GC is still often used in clinical practice to treat patients with FM who have gone into cardiogenic shock (Veronese et al., 2021). A retrospective, international, multicentre cohort study showed that 58.5% of patients with NFM and 66.8% of patients with FM received immunosuppressive therapy. GC alone or in combination was the most commonly used drug in both groups (Ammirati et al., 2019). In contrast, clinical studies have indicated that cytotoxic drugs, including cyclosporine and azathioprine, do not improve early or long-term mortality of patients with AM or FM (Chan et al., 1991; Mason et al., 1995). The preliminary results of the Clinical Assessment of New Treatment Regimen for Adult Fulminant Myocarditis trial (NCT03268642) conducted by our center indicated that only three of the 81 patients treated with "life-support based comprehensive treatment regimen (LSBCTR)" (without cytotoxic drugs) died. Compared with

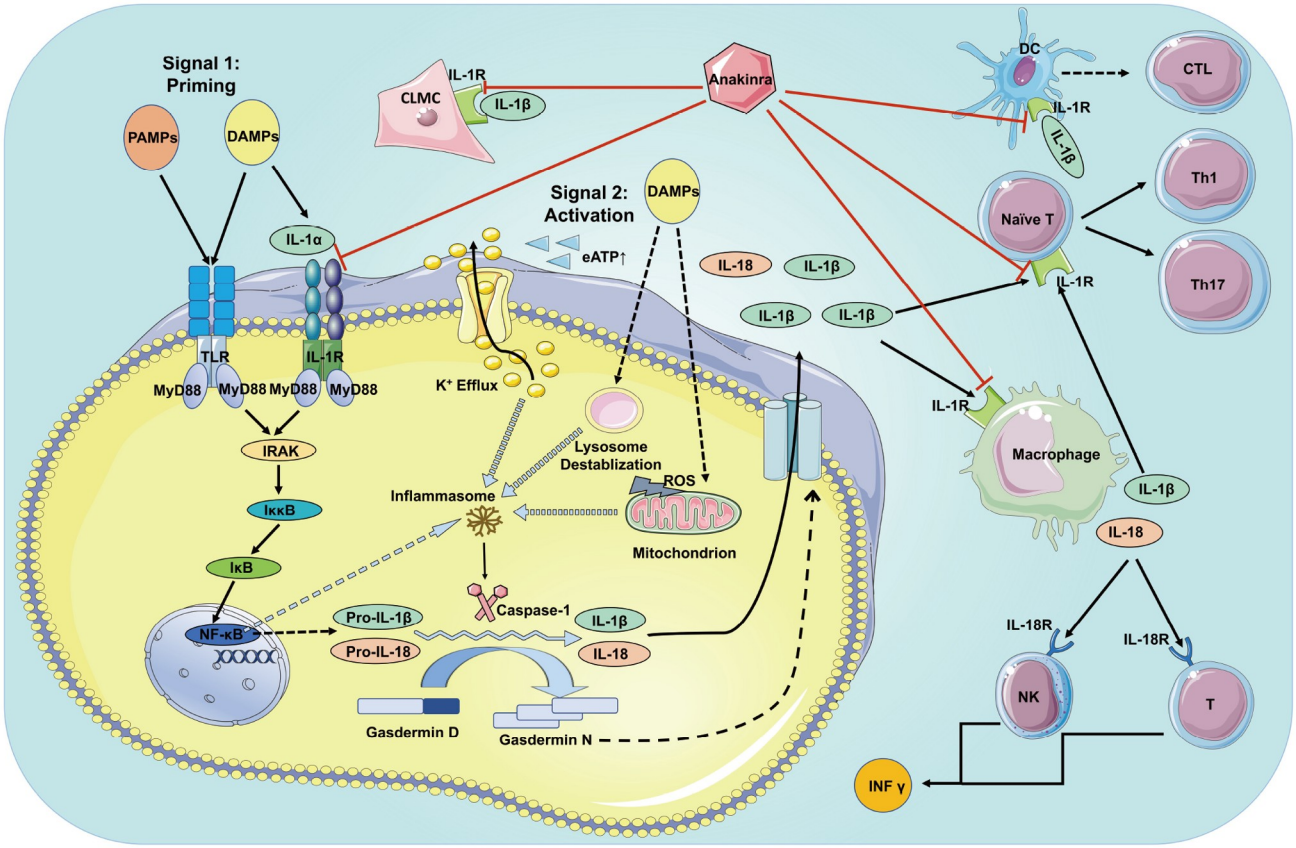

Figure 4 Production of interleukin 1 and the possible mechanism of action of anakinra in myocarditis. IL-1R or TLRs on the cell surface are activated by binding to their respective ligands (signal 1). The TIR domains of these receptors recruit MyD88. MyD88 initiates the cascade of phosphorylated proteins of IRAKs, followed by IκκB and IκB, leading to the phosphorylation of NF-κB. Pro-IL-1β and Pro-IL-18 produced via transcription and translation, enter the cytoplasm. Increased ATP signals lead to K^+ outflow, DAMPs pathway-induced endoplasmic reticulum degradation, and production of reactive oxygen species by mitochondria (signal 2), leading to formation of the inflammasome. Next, Pro-IL-1β and Pro-IL-18 are cleaved into mature IL-1β and IL-18 by active caspase-1. Concurrently, caspase-1 cleaves the N-terminal of Gasdermin D to produce several Gasdermin N subunits, forming plasma membrane pores through which mature IL-1β and IL-18 are released. Anakinra can affect signal 1 by inhibiting the binding of IL-1α to IL-1R. Normally, mature IL-1β promotes the formation of more IL-1β and IL-18 by binding to IL-1R on other macrophages. IL-18 can trigger the production and release of INF-γ by binding IL-18R on NK cells and T cells. IL-1β can also bind to IL-1R on DCs to promote the activation of self-reactive CTL or bind to IL-1R on naïve T cells to affect their differentiation into Th1 and Th17 cells. Anakinra can inhibit the binding of IL-1β to IL-1R on macrophages, DCs, and naïve T cells, thus inhibiting the immune response. Anakinra can also inhibit the accumulation of inflammatory mediators in the heart by inhibiting the binding of IL-1β to CLMCs and attenuating the decrease in CLMCs contractility caused by IL-1β. TIR, Toll/IL-1 receptor; INF, interferon; CMLCs, cardiac lymphatic muscle cells.

routine treatment, "LSBCTR" significantly reduced the in-hospital mortality of patients with FM (3.7% (3/81) *vs*. 46.6% (41/88)) (Li et al., 2019).

However, the Myocarditis Treatment Trial did not distinguish between mortality rates in patients with myocarditis in the acute and chronic phases in the immunosuppression or control groups (Mason et al., 1995). Ammirati et al. (2019) concluded that the long-term outcomes of cardiac death or heart transplantation in patients with FM were significantly higher than at 60 days (71, 43.0% *vs*. 46, 27.8%). In addition, our clinical data showed that approximately 25% of patients with FM had decreased LVEF following discharge from hospital, while patients with slower LVEF recovery during hospitalisation had an increased risk of decreased LVEF after discharge (Jiang et al., 2022). Recently, the 20-year follow-up of TIMIC trial showed encouraging results, indicating that virus-negative inflammatory cardiomyopathy can benefit from 6-month immunosuppressive treatment (prednisone with azathioprine) (Chimenti et al., 2022). These results indicate that the treatment scheme for chronic FM should differ from that of acute FM (Ammirati et al., 2020). Regulating the remaining inflammatory response and protecting cardiac function are vital points that should be considered during the chronic phase. Randomized control trials on myocarditis immunotherapies are currently ongoing (Table 1).

Improved understanding of the mechanisms underlying inflammation and the importance of cytokine storm in myocarditis should result in increased research in immunomodulatory therapy for myocarditis treatment (Wu et al., 2021a). Early effective immune regulation and treatment interventions that inhibit acute inflammation can prevent late cardiac remodelling (Tschöpe et al., 2021). Credible results

Table 1 Ongoing clinical trials of immunotherapy in myocarditis patients

Study name	NCT identifier	Status	Intervention	Type	Mechanism	Phase	Main objection
MYocarditis THerapy With Steroids (MYTHS)	NCT05150704	Recruiting	Methylprednisolone	Corticosteroid	Immunosuppressive therapy	Phase 3	To test the efficacy of pulsed intravenous methylprednisolone versus standard therapy on top of maximal support in patients with acute myocarditis.
Outcome of Steroid Therapy for Myocardial Inflammation in Scleroderma	NCT03607071	Completed	Prednisolone and taper (Other Name: Moderate steroid therapy)	Corticosteroid	Immunosuppressive therapy	Phase 2	To define the cardiac outcome after moderate dose steroid therapy in the scleroderma patients who have myocardial inflammation detection by cardiac MRI.
Study to Evaluate the Efficacy of Immunosuppression in Myocarditis or Inflammatory Cardiomyopathy (IMPROVE-MC)	NCT04654988	Not yet recruiting	Combination therapy: Prednisone, Azathioprine	Corticosteroid, Immunosuppressive agents	Immunosuppressive therapy	Phase 4	To assess the efficacy and safety of 12 months treatment with prednisone and azathioprine comparing to placebo on top of guideline-recommended medical therapy in patients with biopsy-proven virus negative myocarditis or inflammatory cardiomyopathy and reduced ejection fraction (LVEF≤45%).
Myocarditis Treatment Trial	NCT00000524	Completed	Combination therapy: Cyclosporine, Prednisone	Immunosuppressive agents, Corticosteroid	Immunosuppressive therapy	Phase 2	To determine whether immunosuppressive treatment improved cardiac function in patients with biopsy-proven myocarditis.
CZECH-ICIT (CZECH Inflammatory Cardiomyopathy Immunosuppression Trial)	NCT01877746	Unknown	Combination therapy: Prednisone, Azathioprine	Corticosteroid, Immunosuppressive agents	Immunosuppressive therapy	Phase 3	To compare the effect of combined immunosuppressive therapy given on the top standard medical therapy of chronic heart failure according to current guidelines with standard medical therapy of chronic heart failure alone in patients with inflammatory cardiomyopathy.
Micophenolate Mofetil Versus Azathioprine in Myocarditis	NCT05237323	Recruiting	Combination therapy: Mycophenolate mofetil, Methylprednisolone	Immunosuppressive agents, Corticosteroid	Immunosuppressive therapy	Phase 3	To study the direct efficacy of mycophenolate mofetil in combination with methylprednisolonein the treatment of lymphocytic myocarditis.
Study of Muromonab-CD3 and Cyclosporine in Patients With Giant Cell Myocarditis	NCT00027443	Completed	Combination therapy: Muromonab-CD3, Cyclosporine	CD3 Monoclonal antibody, Immunosuppressive agents	Immunosuppressive therapy, Muromonab-CD3 has been shown to reduce the number of lymphocytes and cyclosporine inhibits lymphocyte activation.	Not Applicable	To determine the efficacy of muromonab-CD3 and cyclosporine as treatment in patients with giant cell myocarditis.
Phase II Randomized Study of Muromonab-CD3, Cyclosporine, Methylprednisolone, and Prednisone in Patients With Giant Cell Myocarditis	NCT00004482	Completed	Combination therapy: Cyclosporine, Methylprednisolone, Muromonab-CD3, Prednisone	Immunosuppressive agents, Corticosteroid, CD3 Monoclonal antibody	Immunosuppressive therapy	Phase 2	To assess the effect of immunosuppression with muromonab-CD3, cyclosporine, methylprednisolone, and prednisone versus standard care in terms of death, heart transplantation, or left ventricular assistive device placement in patients with giant cell myocarditis.

(*To be continued on the next page*)

(*Continued*)

Study name	NCT identifier	Status	Intervention	Type	Mechanism	Phase	Main objection
Clinical Assessment of New Treatment Regimen for Adult Fulminant Myocarditis	NCT03268642	Unknown	Combination therapy: intravenous immune globulin; large dose of glucocorticoids; mechanical ventilation; hemodynamic support: intra-aortic balloon pump (IABP) or/and extracorporeal membrane oxygenation (ECMO); continuous renal replacement therapy (CRRT).	Corticosteroid IVIG	Immunomodulatory therapy	Not Applicable	To assess the clinical outcome of patients with fulminant myocarditis (FM) using "Life-support Based Comprehensive Treatment Regimen" and conventional therapy.
Anakinra Versus Placebo for the Treatment of Acute MyocarditIS (ARAMIS)	NCT03018834	Active, not recruiting	Anakinra (Other Name: Kineret)	IL-1 Receptor antagonist	Block IL-1 receptor	Phase 2	To prove Anakinra in addition to standard therapy for treatment of acute myocarditis is superior to standard therapy based on an association of beta-blockers and Angiotensin-Converting-Enzyme inhibitor (ACEI).
CZECH-ICIT (CZECH Inflammatory Cardiomyopathy Immunosuppression Trial) AbataCept for the Treatment of Immune-cHeckpoint Inhibitors Induced mYocarditiS (ACHLYS)	NCT05195645	Not yet recruiting	Abatacept (Other Name: Orencia)	CTLA4 agonists	Inhibit CD80/CD86 mediated T-cell co-stimulation at the level of dendritic-cells, thereby abrogating activation of the T-cells upstream of the CTLA4 and PD-1/PD-L1 pathways.	Phase 2	To study Abatacept for the treatment of ICIs-induced myocarditis. (Find the lowest dose required to achieve a circulating monocytes CD86 receptor occupancy (CD86RO)≥80% within the first week of treatment and sustainably over three weeks)
Effects of Abatacept on Myocarditis in Rheumatoid Arthritis (AMiRA)	NCT03619876	Recruiting	Abatacept (Other Name: Orencia) *vs.* Adalimumab (Other Name: Humira)	CTLA4 agonists	Inhibit CD80/CD86 mediated T-cell co-stimulation at the level of dendritic-cells, thereby abrogating activation of the T-cells upstream of the CTLA4 and PD-1/PD-L1 pathways.	Phase 4	To evaluate the effects of abatacept, a CTLA4-Ig fusion protein that binds CD80/86 (B7-1/B7-2), on subclinical myocarditis in rheumatoid arthritis (RA) through its effect on T cell subpopulations.
Evaluation of G-CSF (Colony Stimulating Factor) in Patients With Chronic Chagas Cardiomyopathy	NCT02154269	Completed	G-CSF (Granulocyte colony stimulating factor)	Adjuvants	Enhance the antigen presentation function of DC	Phase 2	To evaluate the effectiveness of treatment with G-CSF in patients with chronic heart failure secondary to Chagas myocarditis.

from evidence-based medicine are needed to confirm the conclusions reached by previous studies, most of which had small sample sizes, lacked control groups, and included diverse treatment schemes (Canter and Simpson, 2014). In the meantime, immunosuppressive/immunomodulatory therapies should be used with caution within clinical settings. Additionally, efforts should be made to identify more effective immunomodulatory targets and therapeutic drugs. We should also try to determine optimal times for administering immunomodulatory therapies and to identify effective primary endpoints.

Summary and future prospects

We reviewed the aetiology of myocarditis, ICIs- and SARS-CoV-2/COVID-19 vaccine-associated myocarditis, current understanding of immunopathogenesis in VMC, and new perspectives on immunomodulation therapy. However, further basic and clinical researches on myocarditis are required. The aetiology of myocarditis will inevitably broaden as new pathogens and drugs are discovered, requiring changes in the management and long-term prognosis of patients, as well as research and practices on pathogenesis and treatments. The existence of a common immune response or treatment target for myocarditis induced by different causes is worth investigating. VMC is gradually being understood as a typical triphasic disease. However, individual differences and potential key immunopathogenesis of this disease have not been fully elucidated. The boundaries and causes of the transformation between the protective antiviral effects of the immune system and harmful immunopathological damage remain unclear. The detailed mechanism underlying the cytokine storm in FM, and the occurrence of iDCM in some patients also need to be addressed. Thus, we still have a long way to go before fully elucidating the immunopathogenesis of myocarditis.

Additionally, the optimal anti-inflammatory treatment period and immunotherapy targets for myocarditis remain unclear. More effort is required to determine the relationship between myocarditis immunopathogenesis and clinical outcome. Further research is also required to develop more accurate diagnostic methods and to identify effective therapeutic targets. immunomodulatory therapy, consisting of sufficient doses of both GC and IVIG, should be given more attention and should be used to treat FM. Immunosuppressive/immunomodulatory therapy, which has been proven “effective” or “ineffective” against various types of myocarditis in the past, requires in-depth and extensive basic and clinical studies to clarify its mechanisms and the reasons behind its “effectiveness” or “ineffectiveness”. Efforts should also be made to diagnose myocarditis based on its subphenotypes, and precise treatments should be administered based on immunological and pathological typing. Moreover, using advanced single-cell and spatial-temporal RNA-seq technologies can better help us understand the key immunopathogenesis of myocarditis and recognize the crucial points in immunomodulatory therapy, thus providing novel clues for preclinical studies.

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