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INVITED REVIEW

Inflammation and Immunogenetics in Cardiomyopathies: From Molecular Mechanisms to Therapeutic Perspectives

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ABSTRACT

Genetic variants that impair cardiac function or predispose individuals to autoimmune diseases can influence both the risk and severity of inflammatory heart diseases, including lymphocytic myocarditis and cardiac sarcoidosis. We review recent clinical and experimental studies that describe the emerging interplay between genetic susceptibility and active myocardial inflammation. We summarize the current perspective on the mechanisms of inflammatory pathways and gene-immune interactions, and explore the emerging therapeutic approaches aimed at targeting inflammation in genetic cardiomyopathies.

1 | Introduction

Cardiomyopathies comprise a heterogeneous group of primary myocardial disorders in which structural and functional abnormalities cannot be explained by secondary conditions, such as coronary artery disease, hypertension, valvular diseases, or congenital malformations [1, 2]. These conditions are attributable to pathogenic or likely pathogenic genetic variants (PV/LPV) in a relevant proportion of affected individuals [1, 2]. Myocarditis, in contrast, is an inflammatory myocardial disorder meeting established histological, immunological, and immunohistochemical criteria, most frequently because of a viral or autoimmune etiology [3, 4]. Inflammatory cardiomyopathy describes those complicated cases of myocarditis that evolve toward ventricular dysfunction or arrhythmias, thereby reflecting persistent immune-mediated myocardial injury [3, 4]. Traditionally, genetic and inflammatory cardiomyopathies have been categorized as distinct pathophysiological entities [1, 4, 5]. However, recent preclinical evidence and clinical observations suggest a substantial interplay between genetic susceptibility and immunity [6, 7]. Inflammatory "hot-phases" are increasingly recognized in arrhythmogenic cardiomyopathy (ACM), dilated cardiomyopathy (DCM), and non-dilated left ventricular cardiomyopathy (NDLVC), but also in hypertrophic cardiomyopathy (HCM), blurring the boundaries between inherited and acquired cardiac diseases [2, 3]. In this setting, inflammation is not merely a bystander component, but actively contributes to myocyte injury, fibrosis, and adverse remodeling [6, 8]. Indeed, the clinical presentation of cardiomyopathies may overlap with that of myocarditis, with episodes of angina, troponin elevation, myocardial edema, and lymphocytic infiltrates [7, 9–11]. Myocardial inflammation can be non-invasively detected by advanced imaging techniques, such as cardiac magnetic resonance and positron emission tomography, but endomyocardial biopsy is still crucial for defining etiology [3, 4].

These findings underscore the need for a revised vision of cardiomyopathy pathogenesis that integrates genetic and immune mechanisms. A summary is illustrated in Figure 1. This review examines how genetic variants in desmosomal genes (e.g., *DSP*, *PKP2*, and *JUP*) and non-desmosomal genes (e.g., *FLNC*, *LMNA*, and *TTN*) influence and interact with inflammatory pathways, and explores the molecular mechanisms underlying immune activation in genetic cardiomyopathies. It then highlights clinical

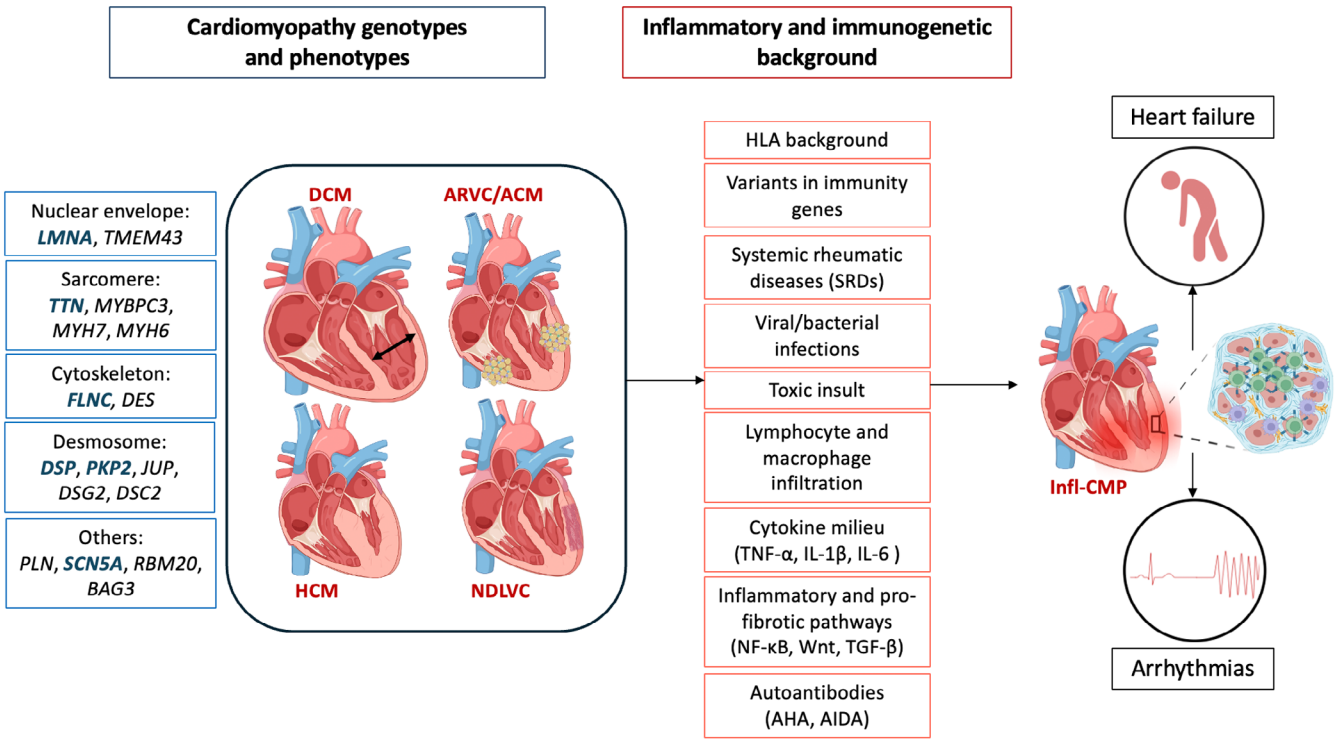

FIGURE 1 | Immunogenetics in cardiomyopathies. The main genotypes and phenotypes associated with myocardial inflammation are summarized. The inflammatory and immunogenetic background influences the development of disease manifestations, including heart failure and arrhythmias. ACM, arrhythmogenic cardiomyopathy; AHA, anti-heart autoantibodies; AIDA, anti-intercalated disc autoantibodies; ARVC, arrhythmogenic right ventricular cardiomyopathy; *BAG3*, BCL2-associated athanogene 3 gene; DCM, dilated cardiomyopathy; *DES*, desmin gene; *DSC2*, desmocollin-2 gene; *DSG2*, desmoglein-2 gene; *DSP*, desmoplakin gene; *FLNC*, filamin C gene; HCM, hypertrophic cardiomyopathy; HLA, human leukocyte antigen; IL, interleukin; Infl-CMP, inflammatory cardiomyopathy; *JUP*, plakoglobin gene; *LMNA*, lamin A/C gene; *MYBPC3*, myosin-binding protein C gene; *MYH6/7*, myosin heavy chain 6/7 gene; NDLVC, non-dilated left ventricular cardiomyopathy; NF-κB, nuclear factor kappa B; *PKP2*, plakophilin-2 gene; *PLN*, phospholamban gene; *RBM20*, RNA-binding motif protein 20 gene; *SCN5A*, sodium voltage-gated channel alpha subunit 5 gene; SRD, systemic rheumatic disease; TGF-β, transforming growth factor beta; *TMEM43*, transmembrane protein 43 gene; TNF-α, tumor necrosis factor alpha; *TTN*, titin gene. Created with BioRender.

scenarios in which this interplay is evident, with implications for risk stratification and targeted therapies, and integrates these insights into a contemporary model of immune-driven heart failure progression and arrhythmogenesis. The overall aim is to provide an updated perspective on the interactions of inflammatory pathways, gene-immune interactions, and emerging therapeutic approaches aimed at targeting inflammation in genetic cardiomyopathies.

2 | Pathophysiology

2.1 | HLA and Immunogenetic Background

The susceptibility to myocarditis and the extent to which inflammation shapes the phenotype of cardiomyopathies are modulated by host immunogenetic background [3]. Among these determinants, human leukocyte antigen (HLA) class II alleles have a central role by governing the repertoire of cardiac and microbial peptides presented to CD4+ T lymphocytes. Distinct HLA haplotypes have been associated with an increased probability of developing myocarditis, cardiomyopathies, or immune-mediated myocardial injury. For example, the HLA-DQ8 (DQA1*0301*/DQB1*0302*) haplotype has been implicated in predisposing to autoimmune myocarditis [12], whereas others may precipitate toxic myocarditis, either induced by the drug clozapine or secondary to mRNA COVID-19 vaccination [13–15]. Alleles such as HLA-DPB1*0901* and HLA-DRB1*1201* are enriched in hepatitis C-associated DCM, implying that antigen presentation by these molecules fosters persistent immune activation [16]. A genome-wide association study identified a locus on chromosome 6p21 within the HLA region in idiopathic DCM, suggesting that the quality and persistence of immune responses to myocardial antigens depend in part on HLA-mediated antigen presentation [17]. A compelling mechanistic illustration comes from molecular mimicry between a peptide from *Bacteroides* species and the human MYH6(614–629) cardiac myosin epitope; this mimic peptide binds permissive HLA-DQA1/B1 molecules and primes autoreactive CD4+ T cells, promoting fulminant myocarditis [18].

HLA haplotypes can shape cardiac involvement in systemic immune-mediated diseases. For example, cardiac sarcoidosis has been linked to HLA-DQB1*0601*, an allele that may promote abnormal antigen-driven inflammation [19, 20]. In patients who appear to have both cardiac sarcoidosis and ACM in overlap, HLA-mediated immune response to environmental triggers may contribute to disease expressivity [21].

Beyond HLA, variants in immune regulatory genes such as *IL12RB1* and *TLR3* increase susceptibility to bacterial and viral myocarditis and influence the progression toward DCM, likely impairing pathogen sensing or resolution of inflammation [22, 23]. Findings of rare immune gene variants in patients who also carry cardiomyopathy-causing variants suggest that combined genetic burdens in immune and structural pathways can amplify inflammatory risk [24]. These observations support a model in which immunogenetics modifies penetrance and severity of cardiomyopathy, determining whether a structural genetic variant produces a predominantly mechanical phenotype or instead manifests as recurrent inflammation. On the horizon, HLA genotyping or including immune genes in testing panels may help to refine stratification for myocarditis and cardiomyopathies [6].

2.2 | Circulating Cytokines

Pro-inflammatory cytokines constitute a major mechanistic interface between genetic myocardial vulnerability and immune activation. Cytokines can impair cardiomyocyte contractility, disrupt calcium homeostasis, suppress β-adrenergic signaling, and stimulate the turnover of key sarcomeric, cytoskeletal, and desmosomal proteins, contributing to heart failure and arrhythmogenesis [25, 26].

Interleukin (IL)-1β works as a central pro-inflammatory signal, regulating downstream immune pathways and directing leukocyte trafficking to sites of myocardial injury [27]. IL-1β promotes adverse structural remodeling, exerts negative inotropic effects, and induces myocyte apoptosis, and its inhibition in animal models slows progression to clinically manifest disease [28]. IL-1β requires NLRP3 inflammasome activation, which has been involved in acute myocarditis pathogenesis [29, 30]. Apoptosis has also been described as a mechanism in myocarditis and "hot-phase" ACM [31–33].

IL-6 is another main pro-inflammatory cytokine consistently elevated in myocarditis and cardiomyopathies, which promotes fibroblast activation [34, 35]. Inflammation also exerts direct and indirect cellular effects that promote arrhythmias [26].

In DCM patients, a network of cytokines, including IL-1β, IL-6, and TNF-α, is overexpressed and contributes to ventricular dilation, systolic dysfunction, and progressive maladaptive remodeling [36, 37]. In ACM patients, myocardial expression of IL-17 and TNF-α and elevated circulating levels of IL-6R, IL-8, MCP1, and MIP1β were observed [38]. In parallel, a cytokine milieu can induce ACM features in healthy cardiomyocytes [38]. These examples illustrate how chronic subclinical inflammation may slowly exacerbate a genetic cardiomyopathy phenotype.

Other inflammatory biomarkers are currently under investigation. For example, galectin-3 is variably expressed in patients with HCM, DCM, and myocarditis, in which promotes systolic dysfunction and correlates with myocardial inflammation and/or fibrosis [39, 40]. Pentraxin 3 (PTX3) is markedly increased in patients with myocarditis, with circulating levels correlating with heart failure, and is expressed in epicardial pro-inflammatory fibroblasts of an ACM mouse model [41, 42]. Bone morphogenetic protein 4 (BMP4) availability in the cardiac microenvironment was shown to control inflammation and fibrosis in autoimmune myocarditis [43].

2.3 | Intracellular Signaling Pathways

Innate immune signaling pathways activation appears to be a common denominator in most cardiomyopathies. A key regulator is the nuclear factor kappa B (NF-κB), which drives the production of pro-inflammatory cytokines and chemokines and the subsequent recruitment of immune cells [8]. NF-κB becomes aberrantly activated in cardiomyocytes carrying certain genetic variants as a final unifying pathway across different genotypes and phenotypes. In a preclinical model where NF-κB signaling was constitutively activated in cardiomyocytes, mice developed DCM with excessive myocardial inflammation and myocyte atrophy, which was reversible by NF-κB suppression [44]. NF-κB is also abnormally functional in DCM and end-stage HCM [45–49]. The NF-κB canonical pathway is pathologically activated in models of *JUP*, DSG2, and *PKP2* ACM, as indicated by an increased nuclear accumulation of phospho-RelA/p65 subunit [50]. This mechanism triggers the release of cytokines, such as TNF-α, IL-1β, and IL-6, and chemokines that attract lymphocytes and macrophages, contributing to ACM phenotype. Several findings suggest that affected cardiomyocytes can initiate an inflammatory cascade themselves via NF-κB. Notably, NF-κB blockade alleviated disease features, confirming that cytokine-driven inflammation is not merely epiphenomenal but causative [50, 51].

Another pathway involved in cardiomyopathies is transforming growth factor β (TGF-β), which is strongly pro-fibrotic and stimulates collagen deposition and scar formation. TGF-β is often activated downstream of inflammation. In ACM, overactivated TGF-β1 and p38 mitogen-activated protein kinase (MAPK) signaling can lead to extensive fibrosis that further injures cardiomyocytes and perpetuates inflammation [52]. *TGFB3* was deemed a causative variant in a family with ACM, reinforcing its role in pro-fibrotic transcriptional programs [53, 54].

Glycogen synthase kinase 3 beta (GSK3β), a kinase in the Wnt/β-catenin pathway, also plays a role in cardiomyopathies. At baseline, GSK3β activity suppression enhances Wnt signaling and promotes maladaptive remodeling characterized by increased ventricular fibrosis, dysfunction, and hypertrophy [55, 56]. On the contrary, in disease conditions, GSK3β inhibition exerts cardioprotective and anti-fibrotic effects. In ACM, GSK3β is constitutively activated and mislocalized at the site of intercalated disc, causing cardiomyopathy and inflammatory features, which are reverted by its inhibition [55, 56].

Inflammation and neurohormonal pathways, such as sympathetic activation and the renin-angiotensin-aldosterone system (RAAS), which are responsible for maladaptive remodeling, can amplify one another [25]. Elevated catecholamines and angiotensin II, as part of heart failure physiology, can potentiate inflammatory signaling and subsequent fibrosis. For example, angiotensin II directly stimulates NF-κB and cytokine release from cardiac cells. In an animal model, NF-κB inhibition ameliorated angiotensin II-induced cardiac inflammation and damage

[57]. Thus, once heart failure begins, it can feed back to worsen inflammation and vice versa, creating a self-perpetuating cycle.

2.4 | Immune Cells

Myocarditis is defined by an infiltrate of ≥14 leukocytes/mm^2, with up to 4 monocytes/mm^2, and ≥7 CD3-positive T lymphocytes/mm^2, usually associated with cardiomyocyte necrosis [3, 58]. Pathologically, inflammatory cells are found in cardiac samples of a large part of cardiomyopathy patients. Autopsy and biopsy studies showed the presence of patchy inflammatory infiltrates composed mainly of T lymphocytes and macrophages in patients with DCM [3, 59–61] and, intermixed with the fibrofatty replacement in patients with ACM [62, 63]. These infiltrates sometimes fulfill the Dallas criteria for active myocarditis, meaning that there is ongoing myocyte necrosis with inflammation, although often the inflammatory foci are small and do not cause obvious necrosis. Regulatory T cells (Treg), expressing IL-32, may also contribute to pathologic remodeling in ACM [64].

Moreover, infiltrating macrophages can interpose between myocytes, release IL-1β, nitric oxide, and other reactive species that electrically uncouple cells, fostering conduction block and reentry arrhythmias [65, 66]. There is evidence that macrophages can even electrically couple with cardiomyocytes via gap junctions, contributing to ectopic activity [67]. In ACM, CCR2+ monocyte-derived macrophages, activated by NF-κB, localize to damaged areas and exacerbate myocyte death, fibrosis, and arrhythmias, and their suppression alleviated ACM phenotype [51]. Fibroblasts expressing fibroblast activation protein (FAP+) are associated with fibrosis and systolic dysfunction [68]. In cardiomyopathies and heart failure, CCR2+ macrophages drive FAP+ fibroblasts accumulation via IL-1β signaling [69].

2.5 | Autoantibodies

The presence of circulating autoantibodies in both myocarditis and cardiomyopathy patients and preclinical models demonstrates that a chronic immune response can induce or worsen cardiac phenotypes over time.

Organ- and disease-specific serum anti-heart autoantibodies (AHA), directed against most cardiac antigens, are frequently found in virus-negative, autoimmune myocarditis [3, 59]. Immunization of genetically susceptible mice with human cardiac myosin can induce experimental autoimmune myocarditis [70]. Furthermore, human AHA proved to be directly pathogenic, since its passive transfer can induce myocarditis in BALB/c mice [71]. AHA positivity represents a biomarker of autoimmunity in myocarditis, correlates with adverse outcomes, and can predict the response to immunosuppressive treatment [72–74].

AHA is also found in patients with DCM and even in their asymptomatic relatives [59, 75, 76]. During follow-up, AHA can predict the evolution to clinical DCM [77].

AHA and anti-intercalated disc autoantibodies (AIDA) are present in patients with ACM and cases of arrhythmic myocarditis [72, 76–78]. For example, anti-desmoglein-2 antibodies correlated with disease severity in ACM patients and caused arrhythmias and myocardial damage in animal models by disrupting desmosomal and gap junction integrity and contributing to electrical instability [79]. These autoantibodies could be pathogenic, causing ongoing myocyte injury or arrhythmias, or they might be biomarkers of an underlying immune dysregulation [80]. In any case, their presence supports the idea of an inherited autoimmune tendency.

2.6 | Exogenous Triggers

Viral infections can cause myocarditis and precipitate cardiomyopathies [81]. For example, coxsackievirus CVB3 increases TNF-α and downregulates the expression of connexins 43 and 45 [82].

Strenuous physical activity is another modulator of disease penetrance and expressivity. In the ACM preclinical model, physical exercise is associated with inflammation and fibrosis progression [56, 83, 84]. In patients with ACM, either with or without desmosomal variants, high-intensity exercise can worsen the phenotype severity and trigger the “hot-phases” [85–87]. In patients with active myocarditis, uncontrolled physical exercise should be avoided during the acute phase, since it could induce ventricular arrhythmias and slow inflammation resolution [88, 89].

Alcohol is a known cardiac stressor, and its abuse can cause ventricular dilation and dysfunction, even in normal hearts [90]. However, alcohol-induced cardiomyopathy may conceal genetic variants in DCM-associated genes, especially in the *TTN* gene [91]. In ACM preclinical models, alcohol consumption increased myocardial fibrosis and ventricular arrhythmias [92].

Cancer-related drugs, especially standard chemotherapy, are associated with cardiac toxicity. However, variants in *TTN* predispose to increased adverse events to anthracycline, as compared with genotype-negative patients with cancer [93]. Myocarditis is also a consequence of immune-checkpoint inhibitors, but the genetic background in its susceptibility is still unknown [94].

Pregnancy, itself associated with changes in immune status and hemodynamic balance, may unmask concealed genetic cardiomyopathies, which are often misdiagnosed as peripartum cardiomyopathy (PPCM) [95].

3 | Arrhythmogenesis and Heart Failure Mechanisms

3.1 | Inflammation in Arrhythmogenesis in Cardiomyopathies

Myocardial inflammation creates an arrhythmogenic substrate through several mechanisms, especially when superimposed on a genetically abnormal myocardium [96]. Inflammation can both acutely trigger ventricular arrhythmias and contribute to long-term electrophysiological remodeling. Cytokines mediate arrhythmias through direct mechanisms, including

prolongation of ventricular action potential duration, impairment of intracellular calcium-handling proteins with spontaneous diastolic calcium release, disruption of connexins and gap junction dysfunction, and promotion of cardiac fibrosis [26].

Cardiotropic viruses can promote arrhythmias by disrupting cardiomyocyte membrane integrity, creating zones of electrical instability that favor triggered activity. Parvovirus B19 and other viruses with endothelial tropism can induce endothelial dysfunction, producing microvascular ischemia that further destabilizes the myocardium [97, 98]. Additional perturbations arise from impaired gap-junctional communication, as in Coxsackievirus B3 models, in which connexin expression and localization become disrupted, thereby slowing conduction and increasing electrical heterogeneity [82].

In virus-negative autoimmune myocarditis, arrhythmogenic mechanisms are more complex and incompletely understood. Giant cells or noncaseating granulomas, by forming mass lesions, represent highly arrhythmogenic infiltrates, whereas in lymphocytic myocarditis, a direct role could be mediated by T lymphocytes [96].

Arrhythmic risk is increased in patients with active lymphocytic myocarditis and cardiac sarcoidosis [99], as well as during the "hot-phases" of ACM and DCM. Indeed, acute myocarditis is a known risk factor for sudden cardiac death in young adults [96]. Myocardial inflammation, proven by imaging and/or histology, proved to be a risk factor for major arrhythmic episodes in NDLVC [100, 101].

During the active inflammatory phase of myocarditis, ventricular arrhythmias are more frequently polymorphic and irregular, reflecting the diffuse dynamic substrate [102]. Ventricular fibrillation may also occur, as seen in fulminant myocarditis or during cytokine storm related to other non-cardiac conditions. This underscores that inflammation can precipitate malignant arrhythmias even in a heart that might otherwise be structurally normal or only mildly affected by fibrosis, especially in genotype-positive individuals [103]. New-onset polymorphic arrhythmias during the natural history of cardiomyopathy should raise suspicion for inflammatory activation or recurrence and prompt further diagnostic and therapeutic assessment [104].

In the post-inflammatory phase, following the resolution of active myocarditis, arrhythmogenic risk substantially reflects the structural consequences of myocardial healing. Fibrosis deposited in areas of prior injury creates regions of impaired conduction that serve as substrates for scar-related ventricular arrhythmias. When fibrosis becomes established, especially if patchy, the resultant alterations in conduction velocity and tissue refractoriness facilitate the development of reentrant circuits. In this non-active inflammatory phase, ventricular arrhythmias are predominantly monomorphic and regular [102]. However, there may be an overlap between arrhythmic features when myocardial inflammation is focal or when fibrosis is very extensive.

Scar localization may orient the etiology and genotype. A subepicardial medium-basal lateral wall substrate is typical of myocarditis, but does not exclude NDLVC, ACM, or DCM, especially in the absence of active inflammation. Isolated left ventricular fibrosis may be consistent with ACM, for example, in *DSP* variant carriers, but associated fibro-fatty replacement and right ventricular involvement often reflect desmosomal gene variants. Septal involvement may be consistent with sarcoidosis, giant cell myocarditis, *LMNA*, or sarcomere variants if associated with hypertrophy [105]. A ring-like scar, involving at least three contiguous segments, should orient toward "high-risk" genotypes such as *DSP*, *LMNA*, and *FLNC* [106–108].

Therefore, in the setting of acute myocarditis, a scar involving the septum, with a ring-like pattern, or accompanied by fatty replacement, should hint at an underlying genetic condition. Additionally, in a progressively evolving substrate, with scar expansion despite the absence of active inflammation, a primary cardiomyopathy has to be excluded.

Bradyarrhythmias may occur, especially when the conduction system is affected by inflammation [96]. Giant cell myocarditis and cardiac sarcoidosis, through compression of septal fibers, often give rise to acute advanced atrioventricular blocks. In lymphocytic myocarditis, bradyarrhythmias may involve selected systemic autoimmune diseases, such as lupus erythematosus, because of an immune injury that may nonetheless preferentially target the conduction tissue. Bradyarrhythmias are also more common in specific genotypes, such as *LMNA*, which has a predominant septal involvement, even in early-stage disease. Inflammation resolution, either spontaneously or after treatment, may revert conduction system disorders, provided that fibrosis is not already established.

Furthermore, inflammation correlates with supraventricular arrhythmias, notably atrial fibrillation [109]. Cytokines, such as TNF-α, promote atrial dysfunction, fibrosis, and arrhythmias [110–112]. For example, myocarditis and cardiac sarcoidosis patients may present with atrial fibrillation or flutter during the acute illness, likely because of atrial cell infiltration [113, 114]. In the post-inflammatory phase, atrial fibrillation is sustained by atrial fibrosis and electrical remodeling, leading to an atrial cardiomyopathy [115]. In HCM, systemic inflammation has been associated with a greater incidence of atrial fibrillation and worse symptoms [46]. Therefore, inflammation can affect all aspects of cardiac rhythm, not just ventricular arrhythmias.

3.2 | Inflammation and Heart Failure in Cardiomyopathies

Inflammation is a major modifier of heart failure progression in cardiomyopathies, acting through both direct and indirect mechanisms. Pro-inflammatory cytokines depress myocardial contractility, promote fibroblast activation, often via TGF-β signaling, and induce cardiomyocyte loss through immune-mediated cytotoxicity and programmed cell death pathways [37]. The cumulative effect is a reduction in contractile mass and ventricular compliance. When inflammatory episodes recur or persist at low grade, progressive cardiomyocyte loss occurs, with injured regions replaced by fibrotic tissue. This process increases ventricular stiffness, elevates filling pressures, and compromises systolic performance. Over time, diffuse fibrosis may

lead to restrictive physiology or accompany chamber dilation secondary to wall thinning.

Acute inflammatory flares can precipitate transient heart failure decompensation on a background of chronic cardiomyopathy and are associated with adverse prognosis. In genetically determined cardiomyopathies such as those related to *DSP* or *FLNC* variants, myocarditis-like episodes may produce characteristic patterns of subepicardial or ring-like scarring, with each inflammatory insult contributing incrementally to myocardial damage. In some cases, heart failure exacerbations may reflect a shared inflammatory trigger, such as viral infection, rather than irreversible structural progression. Importantly, resolution of inflammation has been associated with reverse remodeling and recovery of systolic function, highlighting its potential reversibility [116].

The phenotype of inflammation also influences heart failure expression. Granulomatous diseases such as cardiac sarcoidosis can produce extensive fibrosis and focal wall thinning, whereas fulminant inflammatory processes, including giant cell myocarditis, may cause rapid cardiomyocyte necrosis and acute pump failure. Conversely, persistent low-grade lymphocytic inflammation can prevent reverse remodeling in genetic dilated cardiomyopathy, maintaining a state of chronic dysfunction even in the absence of overt disease progression.

Assessment of myocardial inflammation, therefore, carries prognostic significance. Active inflammation identifies a subset of patients with elevated short-term risk for decompensation, but also with greater potential for functional recovery if inflammation is effectively controlled. By contrast, persistent inflammatory infiltrates or viral genome retention are associated with poorer recovery of left ventricular function and increased likelihood of progression toward dilated cardiomyopathy. Fibrosis burden, as detected by late gadolinium enhancement on cardiac magnetic resonance imaging, serves as an integrated marker of cumulative inflammatory injury and strongly predicts malignant progression [117, 118].

Not all genetic variants confer the same heart failure risk. Genotype-positive patients have worse outcomes than those with negative genetic testing [119]. *TTN* variants, although common in DCM, have variable penetrance since many carriers never develop heart failure and are influenced by external stressors. Instead, heart failure penetrance is higher in patients with *LMNA* variants, or multiple sarcomere variants may exacerbate symptoms [120]. Likewise, variants in *RBM20* or *BAG3* can lead to severe, early-onset DCM with a high likelihood of rapid progression to end-stage heart failure [121, 122]. *FLNC* truncating variants confer a high risk of rapid HF progression, often presenting as severe DCM in young adulthood with extensive fibrosis [123]. In desmosomal ACM, heart failure usually occurs later and is mostly related to left ventricular or biventricular involvement [124].

These observations underscore that a genotype-based classification can help predict outcomes better than phenotype alone, hinting that in the future, heart failure prognostication will integrate genomic and inflammation data [109].

Inflammation significantly increases heart failure and arrhythmic risk in cardiomyopathies, sometimes independently of baseline structural abnormalities. Once the inflammation resolves, the risk may revert to that dictated by their chronic scar burden, contractile reserve, and genetic substrate. Reducing inflammation can be a crucial component of heart failure and arrhythmia prevention. This interplay emphasizes that the risk of mechanical and electrical adverse events is not static and can be influenced by myocardial inflammatory activity. Identifying and treating inflammation in patients with cardiomyopathies, therefore, becomes a crucial component of heart failure arrhythmia management and prevention. In summary, the presence of inflammation adds a layer of dynamic risk in cardiomyopathy: it can mean higher short- and long-term risk, but also a modifiable factor that can change the disease trajectory if addressed.

4 | Cardiomyopathy-Associated Genes and Immune Mechanisms

The progression from myocardial inflammation to clinically overt cardiomyopathy is not homogenous across patients. Instead, it reflects the interaction between the nature of genetic variants, the intensity and chronicity of immune activation, and the degree to which inflammatory processes remodel myocardial architecture. Genetic variants affecting the sarcomere, cytoskeleton, desmosomes, nuclear envelope, or ion-handling systems intersect with immune mechanisms in characteristic ways. Inflammation, in turn, accelerates the development of systolic dysfunction, dilation, and arrhythmogenic remodeling. This reciprocal relationship, with genotype influencing immune behavior and immune activation shaping cardiomyopathic progression, represents one of the central themes in contemporary understanding of inflammatory cardiomyopathies.

A wide range of cardiomyopathy-causing variants converge on final pathways involving cell death, cytoskeletal collapse, intercalated-disc disassembly, mitochondrial dysfunction, and electrical uncoupling. Yet many of these variants also influence how the immune system perceives and reacts to myocardial stress, determining whether an inflammatory episode resolves fully, partially, or not at all. Genetic background, therefore, acts as both a determinant of myocardial fragility and a regulator of immune threshold and resolution, making certain individuals more susceptible to transitioning from acute myocarditis into chronic inflammatory cardiomyopathy or dilated phenotypes. Genotype-specific inflammatory molecular mechanisms are summarized in Figure 2.

4.1 | Structural Genes

Dystrophin (*DMD*) is crucial for maintaining membrane integrity, preventing contraction-induced damage, and cell-signaling. Dystrophin deficiency, as in X-linked DCM from *DMD* variants, causes membrane instability and chronic muscle injury, leading to loss of cytoskeletal support and persistent immune cell infiltration in both skeletal muscle and heart [125]. In Duchenne muscular dystrophy (DMD), myocardial

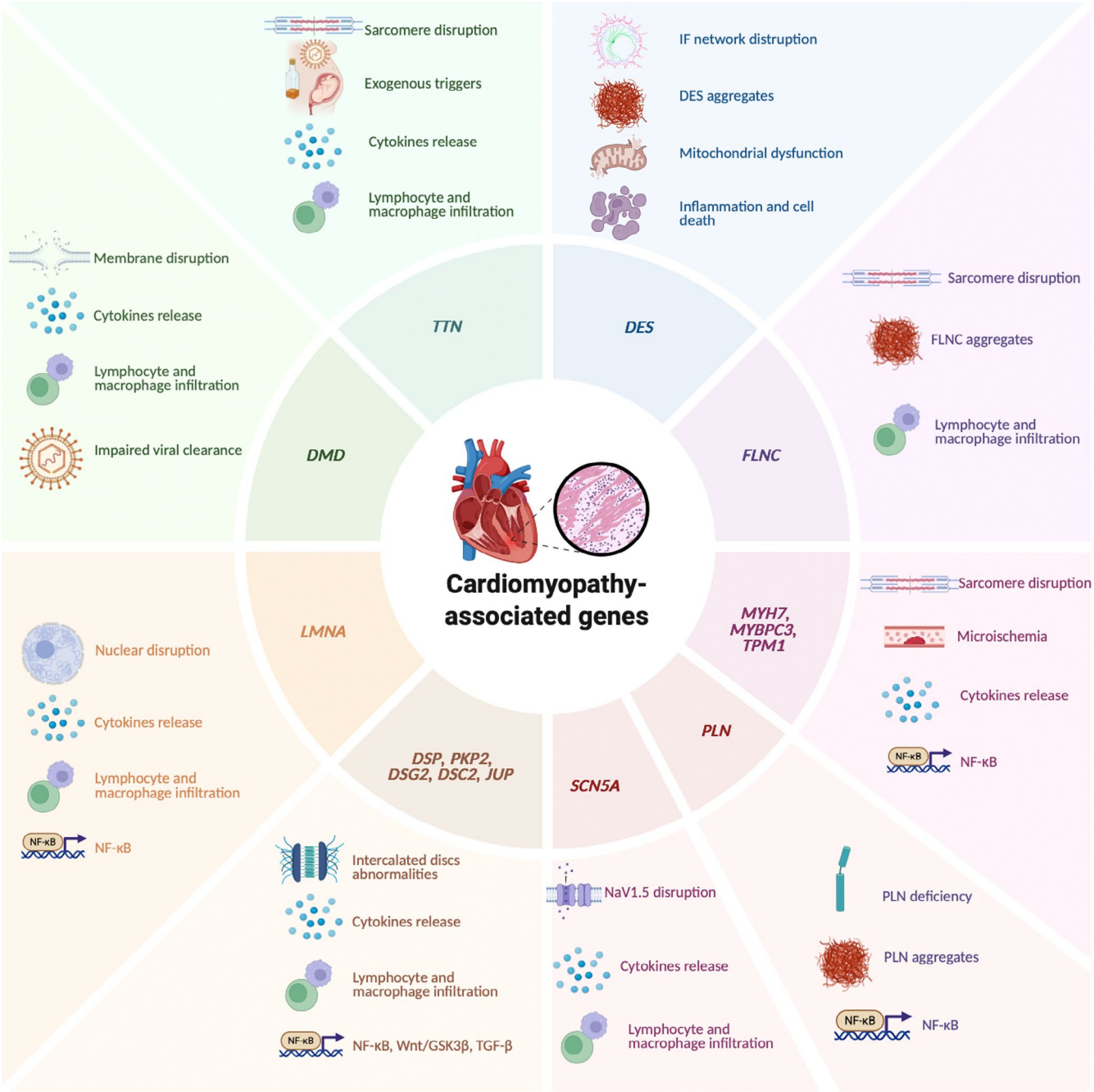

FIGURE 2 | Genotype-specific inflammatory molecular mechanisms. The main molecular inflammatory mechanisms, divided by each cardiomyopathy-associated gene, are represented. *DES*, desmin gene; *DMD*, dystrophin gene; *DSC2*, desmocollin-2 gene; *DSG2*, desmoglein-2 gene; *DSP*, desmoplakin gene; *FLNC*, filamin C gene; GSK3β, glycogen synthase kinase 3 beta; IF, intermediate filaments; *JUP*, plakoglobin gene; *LMNA*, lamin A/C gene; *MYBPC3*, myosin-binding protein C gene; *MYH7*, myosin heavy chain 7 gene; NF-κB, nuclear factor kappa B; *PKP2*, plakophilin-2 gene; *PLN*, phospholamban gene; *SCN5A*, sodium voltage-gated channel alpha subunit 5 gene; TGF-β, transforming growth factor beta; *TPM1*, tropomyosin 1 gene; *TTN*, titin gene. Created with BioRender.

inflammation precedes fibrosis and contributes substantially to systolic dysfunction [126]. Indeed, *Dmd*-mutant animal models show leukocyte and macrophage infiltration in the myocardium [127, 128]. Clinically, patients with *DMD* variants have been noted to retain viral genomes in the myocardium and have worse outcomes after viral myocarditis, resulting in chronic inflammatory cardiomyopathy, possibly because viral clearance and myocardial healing are impaired in the *DMD*-deficient heart [126, 129, 130].

Filamin C (*FLNC*) is mainly localized at Z-discs, where it cross-links actin to anchor thin filaments [123]. Truncating variants in *FLNC* are mostly responsible for DCM, ACM, NDLVC, LVNC, and restrictive cardiomyopathy (RCM), as well as skeletal myopathy, whereas missense variants are associated with HCM, with a possible overlap [131, 132]. *FLNC* variants, either by haploinsufficiency or misfolding, cause sarcomere disorganization, with saturation of lysosome-mediated autophagy, and accumulation of filamin C and its binding partners; proteotoxic

damage occurs in cardiomyocytes, culminating in cytokine upregulation and inflammation [133, 134]. *FLNC* is considered among "high-risk" genes, and malignant arrhythmic events should be expected on the basis of older age, male sex, previous syncope, nonsustained ventricular tachycardia, and even only mildly reduced LVEF [1, 135]. Active myocarditis was proven, both by imaging and histology, in patients with *FLNC* variants from various cohorts [7, 136]. Remarkably, arrhythmic and sudden cardiac death risk appeared to be increased during the "hot-phases", with a possible viral "second-hit" in some cases [136].

Desmin (*DES*), an intermediate filament protein, is responsible for maintaining the equilibrium among most cellular components necessary for proper mechanochemical signaling, organelle cross-talk, energy production, and trafficking processes required for proper tissue homeostasis [137]. Most *DES* variants determine a loss-of-function, leading to the disruption of the cellular network [138, 139]. Abnormalities of mitochondria, such as structural disorganization, swelling of cristae, and impaired oxidative phosphorylation, represent a hallmark of *DES*-related diseases [140]. Mitochondrial dysfunction acts as a canonical trigger for innate immune activation, generating reactive oxygen species and releasing mitochondrial DNA that can engage cytosolic pattern-recognition receptors, thereby facilitating a state of chronic inflammatory sensitization. In *Des*-deficient mice, extensive inflammatory infiltration and fibrosis, together with increased expression of osteopontin and galectin-3, was observed [141]. In a mouse model of TNF-α-induced cardiomyopathy, TNF-α-mediated activation of caspases promotes proteolytic cleavage of desmin, aggregate formation, and loss of intercalated disc localization, eventually leading to mitochondrial dysfunction, cell death, and heart failure [142]. Another proposed pathophysiological mechanism is a gain-of-function, with protein misfolding and aggregation, activating a cellular stress response with cytokine upregulation and inflammasome activation. On the basis of genetic variant localization and cellular structures involved, *DES*-related phenotypes encompass DCM, RCM, ACM, PPCM, and skeletal myopathy. Malignant arrhythmic events are predicted by male sex, nonsustained ventricular tachycardia, and LVEF < 50% [143].

4.2 | Sarcomeric Genes

Titin (*TTN*), the largest protein in the human proteome and a central determinant of structural integrity, passive elasticity, and force transmission in myocytes, represents a nexus between mechanical stress and inflammatory signaling [144, 145]. Truncating variants in *TTN* (*TTN*tv) are the most prevalent cause of DCM, which is an abnormal dilation and dysfunction of ventricular chambers, accounting for 25% of familial and 18% of isolated cases [146].

Cytokine-driven alterations in titin post-translational modifications, such as increased phosphorylation of the N2B region or oxidation-induced stiffening of compliant elements, can magnify the mechanical consequences of *TTN*tv and unmask latently compensated disease [36]. Systemic inflammation in *TTN*tv carriers can precipitate acute decompensation and arrhythmogenesis by inducing proteolytic cleavage of titin, producing fragments that may serve as danger-associated molecular patterns (DAMPs) and further amplify innate immune responses [147, 148]. These observations suggest that titin is not only a mechanosensor, but also an immunomodulatory substrate capable of linking genetic perturbations to inflammatory cascades. Active myocarditis can be associated with *TTN*tv and is usually complicated by severe heart failure and ventricular arrhythmia triggered by active myocarditis, underscoring that inflammation can precipitate acute disease in genetically susceptible myocardium [149]. Lymphocytic myocarditis is also frequently found in myocardial biopsies of patients with genotype-negative DCM, termed inflammatory DCM, with evidence of cardiac viral genomes in some cases [3]. Evidence of systemic autoimmune diseases, including systemic lupus erythematosus or rheumatoid arthritis, and inflammatory triggers are found in a subset of DCM patients, both with and without *TTN*tv [150, 151], suggesting that among both genetic and idiopathic DCM cases, a subset has inflammation as a major contributor to disease phenotype. As previously discussed, several secondary factors, including alcohol, drugs, and pregnancy, can contribute to DCM onset and outcomes, proving a "double-hit" model [152].

Other sarcomeric genes, such as **myosin heavy chain 7 (*MYH7*)** and **myosin-binding protein C (*MYBPC3*)**, are classically associated with HCM; however, variants in other sarcomeric genes, or the presence of multiple combined variants, may result in DCM or RCM. HCM has not traditionally been linked to inflammation as directly as DCM or ACM, since its pathogenesis is dominated by myocardial hypertrophy and myofiber disarray with interstitial fibrosis, largely because of chronic biomechanical stress and microvascular ischemia, rather than lymphocytic myocarditis [153]. Microvascular dysfunction, with hypertrophied walls and narrowed intramyocardial arterioles, leads to ischemia, especially during exercise [154, 155]. This repetitive ischemia can cause small myocardial injury events, with macrophages and other immune cells that will transiently appear to clear debris. Thus, an HCM heart may have an ongoing low-grade inflammatory process secondary to microinfarction, though not an autoimmune or primary inflammatory condition [154, 155]. This process likely contributes to the replacement fibrosis seen in HCM, particularly in the mid-myocardium of the hypertrophied septum. In a sense, the inflammation here is reactive, not the fundamental driver of HCM, but it might still influence the clinical course by promoting fibrosis and arrhythmias. Patients with end-stage HCM, where systolic function finally declines after years of hypertrophy, often show elevated circulating inflammatory cytokines, such as IL-6 and TNF-α, as well as the presence of neutrophil extracellular traps (NETs) [153, 156]. As compared with early HCM, higher IL-6 levels in advanced HCM suggest either activation of inflammatory pathways as part of disease progression, or a consequence of heart failure and tissue injury [157]. In a mouse model recapitulating *MYBPC3*-related DCM, M1 macrophages and IL-6 were increased, along with a pro-inflammatory transcriptional profile [158]. Histologically, myocardial biopsies in HCM related to **α-tropomyosin (*TPM1*)** variants can show small foci of mononuclear inflammatory cells around areas of replacement fibrosis, or small intramyocardial scars from microinfarctions because of microvascular disease, but not multifocal T cell infiltrates typical of acute myocarditis [46].

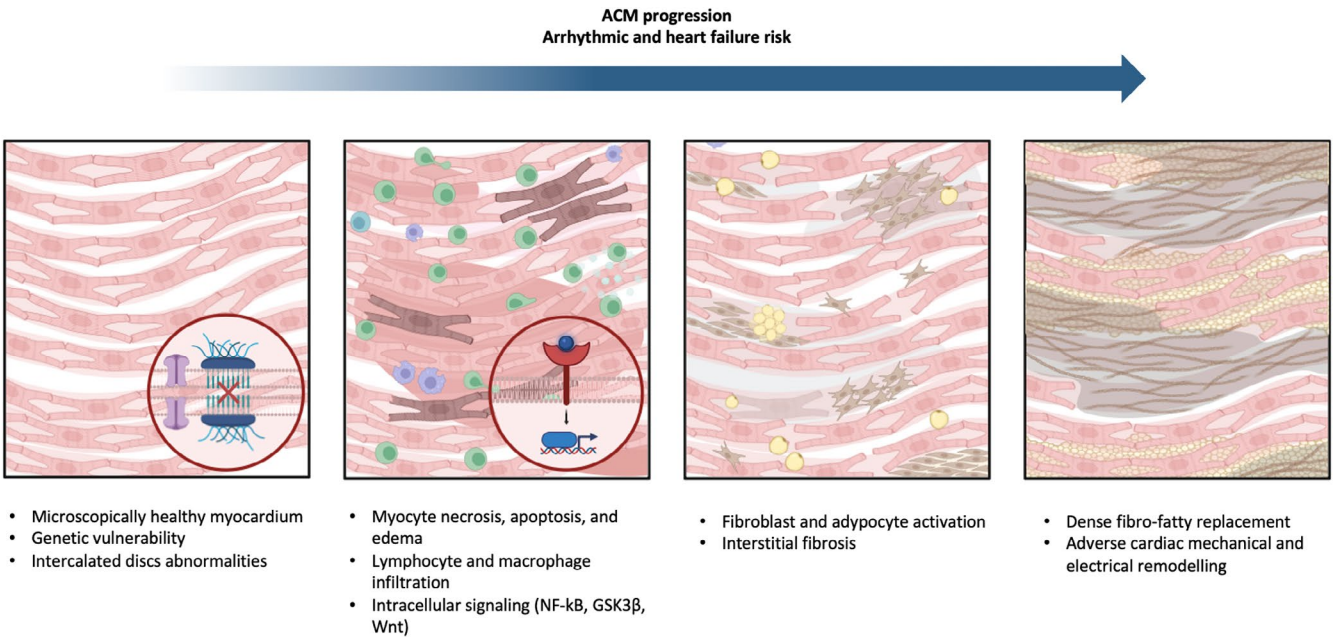

FIGURE 3 | Arrhythmogenic cardiomyopathy and inflammation. The natural history of desmosomal ACM and the role of inflammation are depicted, ranging from subclinical molecular abnormalities to symptomatic fibro-fatty replacement. ACM, arrhythmogenic cardiomyopathy; GSK3β, glycogen synthase kinase 3 beta; NF-κB, nuclear factor kappa B. Created with BioRender.

High-sensitivity C-reactive protein and NF-κB activation in cardiomyocyte nuclei correlate with the degree of hypertrophy and the extension of fibrosis [46]. Indeed, higher levels of inflammatory markers in HCM are associated with worse diastolic function and more fibrosis, and one longitudinal study found that baseline NF-κB activity in myocardium predicted heart failure progression in HCM over a decade of follow-up [47]. In HCM, age, wall thickness, atrial dilation, obstructive outflow gradients, family history of SCD, NSVT, and previous syncope predict malignant arrhythmic events [159]. However, imaging-proven active inflammation in HCM was significantly associated with ongoing myocardial injury, represented by persistent troponin release, and increased risk of sudden cardiac death [160, 161].

In HCM phenocopies, inflammation is also a feature. In Fabry disease, because of *GLA* variants, lyso-Gb3 deposition triggers macrophage activation and inflammatory response in cardiac tissue [162]. In transthyretin amyloid cardiomyopathy, there can be immune cell infiltration, as well as a chronic inflammatory milieu in some forms, triggering the activation of antibody production in some cases [163]. Additionally, inflammation plays a central role in forms of acquired RCM, such as eosinophilic myocarditis, endomyocardial fibrosis, and radiation-induced cardiomyopathy [164].

4.3 | Desmosomal Genes

Desmosomes are responsible for the electro-mechanical coupling between cardiomyocytes and constitute intercalated discs [165]. Desmosomes are central in arrhythmogenic cardiomyopathy (ACM), which is a "scarring" disease, characterized by fibro-fatty myocardial replacement, with a classic right-dominant (ARVC), left-dominant (ALVC, or NDLVC), or biventricular involvement. It is primarily a genetic disease of the cardiac desmosomes, typically manifesting with ventricular arrhythmias, fibrofatty myocardial replacement, and risk of sudden death, often in young individuals and athletes. Remarkably, "hot-phases" of myocardial inflammation are most prevalent in desmosomal ACM among other genotypes and phenotypes. In patients with recurrent myocarditis, with bursts of chest pain and troponin release, underlying ACM should be suspected, especially in the presence of a familial history, extensive scar, and ventricular arrhythmias as "red flags". Pathogenic variants in desmosome genes disrupt cell–cell adhesion in the heart, and this electro-mechanical uncoupling leads to cardiomyocyte injury and loss, fibrosis, as well as inflammation because of immune cells' recruitment and signaling pathways [165]. The progression of ACM is represented in Figure 3.

Plakoglobin (*JUP*) strengthens cell–cell adhesion, stabilizes desmosomes, and modulates signaling pathways that contribute to tissue development and structural integrity. In ACM patients, plakoglobin expression, together with NaV1.5 and Cx43, is reduced at the site of intercalated discs [166, 167]. In parallel, loss of junctional plakoglobin immunoreactivity was observed also in giant cell myocarditis and cardiac sarcoidosis, but not in lymphocytic myocarditis [38]. Remarkably, exposure of neonatal rat ventricular myocytes to IL-17, TNF-α, and IL-6 causes plakoglobin redistribution at the intracellular level [38]. In a zebrafish model of ACM with cardiac myocyte-specific expression of $JUP^{2157del2}$, inhibition of GSK3β by SB216763 restored the regular localization of plakoglobin, Cx43, and NaV1.5 [55]. In mice and neonatal rat ventricular myocytes expressing $JUP^{2157del2}$, SB216763 could reduce myocardial inflammation and prevent ACM progression [56]. In the same model, an abnormal activation of the NF-κB pathway was evident, and its inhibition by Bay11-7082 produced the same beneficial effects

[50]. All these findings showed that ACM features a cardiomyocyte cell-autonomous immune activation [50]. Interestingly, cardiac innate immune signaling findings were recapitulated in buccal mucosa cells of ACM patients, in particular during the "hot-phases", and could represent a novel ACM diagnostic tool [168–170].

Desmoglein-2 (*DSG2*) supports desmosomal structure and promotes firm intercellular adhesion, contributing to overall tissue stability and integrity. NF-κB was also activated in *Dsg2*$^{mut/mut}$ mice, which showed clinical and histological features of ACM and release of cytokines and chemokines [50]. Remarkably, Bay11-7082 rescued the disease phenotype and prevented heart failure by reducing inflammation and fibrosis [50]. NF-κB activation in cardiomyocytes of *Dsg2*$^{mut/mut}$ mice led to a myocardial influx of CCR2+ monocyte-derived macrophages, which localized to damaged areas and exacerbated cell death, fibrosis, and arrhythmias [51]. In the same mouse model, inhibition of GSK3β reduced the inflammatory response. Anti-DSG2 autoantibodies have been detected in ACM patients, in whom they correlated with premature ventricular contractions and caused gap junction dysfunction [79]. Similar anti-DSG2 autoantibodies were found in ACM, DCM, and myocarditis, reflecting a shared immune-mediated pathogenesis against desmosomal proteins [171]. Anti-DSG2 autoantibodies were also found in sera of Boxer dogs, which represent a natural model of ACM, in some cases related to striatin (*STRN*) variant, suggesting an autoimmune response can develop secondary to the genetic disease and then further damage the heart [172–174].

Plakophilin-2 (*PKP2*) enhances desmosomal stability to ensure durable cell–cell connections and maintain cardiac tissue structure. NF-κB activation was also observed in human induced-pluripotent stem cells (hiPSCs) derived from *PKP2* patients [50]. In parallel, GSK3β was abnormally activated also in neonatal rat ventricular myocytes expressing *PKP2*^{1851del123}. Although *PKP2*-related disease classically affects the right ventricle, biventricular inflammatory and fibrotic involvement is often observed. Arrhythmic risk in *PKP2* patients, who account for most ARVC patients, includes male sex, age, previous syncope, negative T-waves, premature ventricular complexes, nonsustained ventricular tachycardia, and right ventricular ejection fraction by cardiac magnetic resonance [175].

Desmoplakin (*DSP*) links intermediate filaments to the desmosomal plaque, reinforcing desmosome structure and contributing to the mechanical resilience of tissues. In a transient *Dsp*-deficient zebrafish model, Wnt/β-catenin, TGFβ/Smad3, and Hippo/YAP-TAZ signaling pathways were involved, the first being the most altered and reversible by GSK3β inhibition [176]. In a more recent stable *Dsp*-knock-out, zebrafish showed myocardial structural abnormalities, edema, and bradycardia, which were rescued by SB216763 [83]. A mouse model of *DSP* S311A CRISPR/Cas9-generated knock-in replicated human biventricular ACM [177]. In another mouse expressing *Dsp*$^{R451G/+}$, ACM phenotype manifested only in the presence of a stress trigger [178]. More recently, engineered heart tissues (EHTs) from *DSP*tv-hiPSCs and *DSP*−/− cell line showed basal immune activation and cytokine release, which was further enhanced by Toll-like receptor stimulation, as well as contractile impairment [179]. EHTs' phenotype was improved by colchicine or NF-κB inhibition.

In patients with ACM, among desmosomal genes, *DSP* is the most clinically associated with "hot-phases", which are episodes of myocardial injury and inflammation, with infiltrates of T lymphocytes and macrophages that mimic acute myocarditis [9, 11, 63]. *DSP* variants often cause a left-dominant ACM, with ventricular arrhythmias often preceding overt heart failure [180, 181].

4.4 | Nuclear Genes and Ion Channels

Lamin A/C (*LMNA*) is a major component of the nuclear envelope; gene variants cause a form of cardiomyopathy often characterized by early conduction disease, arrhythmias, and rapid progression to heart failure [182, 183]. Lamins influence gene transcription and chromatin organization, and *LMNA* variants trigger cellular stress pathways. In transgenic mice, mutant lamin A causes an inflammatory cardiomyopathy with marked cardiac NF-κB activity and upregulation of pro-inflammatory genes [45]. Patients with *LMNA* variants had elevated circulating inflammatory cytokines [184]. Myocardial inflammation, either documented by cardiac magnetic resonance or biopsy, was a common feature among *LMNA* carriers and portended worse outcomes [184, 185]. *LMNA* is among cardiomyopathy-associated genes found in patients with arrhythmic myocarditis [7].

LMNA causes a phenotype of NDLVC, or DCM, with worse outcomes as compared with genotype-negative DCM or *TTN*tv. However, *LMNA* carries a high risk of life-threatening malignant ventricular arrhythmias, often when ventricular function is still relatively preserved [182, 186]. Major arrhythmic events are predicted by male sex, non-missense variants, atrio-ventricular blocks, nonsustained ventricular tachycardia, and left ventricular ejection fraction [187, 188].

Transmembrane protein 43 (*TMEM43*), another nuclear envelope protein, is altered in the particularly malignant ARVC type 5 in Newfoundland kindreds. This specific S358L variant leads to cardiomyopathy with documented NF-κB activation and inflammatory cell infiltration in mice [48]. These examples reinforce that even variants in genes not directly part of classical immune pathways can secondarily involve inflammation as part of disease expression. Many *TMEM43* S358L male carriers develop severe cardiomyopathy by mid-life, with prominent heart failure and arrhythmias.

BCL2-associated athanogene 3 (*BAG3*) is a co-chaperone involved in protein quality control and, when mutated, is responsible for proteotoxicity due to the accumulation of damaged proteins and organelles [189]. Mice lacking BAG3 expression do not exhibit marked myocardial inflammation under basal conditions [190]; however, the protein becomes critically relevant once an infectious challenge is introduced. BAG3 expression is induced through NF-κB signaling following exposure to lipopolysaccharide, the principal component of Gram-negative bacterial cell walls, suggesting that BAG3 contributes to the myocardial defense program against bacteria;

its absence in this setting is accompanied by an exaggerated cytokine response [49]. By a complementary overexpression of Tat, a BAG-inhibitor, mice showed increased vulnerability to viral pathogens and progressed to virus-induced inflammatory cardiomyopathy [191], further illustrating that *BAG3* is required for appropriate myocardial adaptation to infectious stress.

Phospholamban (*PLN*) is a calcium-handling protein and, if abnormal, can produce myocardial stress that intertwines with inflammatory signaling [192, 193]. For example, calcium overload because of *PLN* variants can activate calcineurin/NFAT and NF-κB pathways, promoting cytokine expression [194]. In turn, the inflammatory response feeds back, exacerbating cell injury and adverse remodeling. Specifically, the *PLN* R14del variant, which is common among Dutch carriers, can cause an early-onset diffuse cardiomyopathy, often requiring intervention for severe arrhythmias and end-stage heart failure [193, 195].

Sodium voltage-gated channel alpha subunit 5 (*SCN5A*) is well known for channelopathies, such as long QT and Brugada syndromes. There is evidence that *SCN5A* variants can lead to myocarditis-like changes, and conversely, that myocarditis can unmask Brugada patterns in those with *SCN5A* variants [7, 196]. Fever, because of cytokine release, can modulate ion channel expression and enhance Brugada pattern [26]. Some *SCN5A* variants cause a phenotype of progressive conduction block, arrhythmias, and mild ventricular dilation, overlapping with DCM and ACM [196–198]. Autoantibodies against cardiac NaV1.5 sodium channel were recently detected in Brugada syndrome, irrespective of *SCN5A* variant [199].

Ryanodine receptor 2 (*RYR2*) variants are associated with catecholaminergic polymorphic VT (CPVT), an inherited arrhythmia syndrome without baseline cardiomyopathy, but interestingly, some ACM patients were carriers of *RYR2* [200].

To conclude, diverse genotype–phenotype intersections in cardiomyopathy have an immunologic dimension. Desmosomal variants typically provoke intense, episodic myocardial inflammation with local immune cell infiltrates as part of the disease process. Cytoskeletal and nuclear variants often lead to diffuse fibrosis but can also show substantial inflammatory and immune involvement. Sarcomeric variants generally cause disease through mechanical dysfunction, with inflammation as a possible secondary modifier influencing prognosis. All these cases reinforce that genotype can influence immunophenotype: some variants directly activate immune pathways, whereas others create structural instability that makes the heart susceptible to immune-mediated damage under stress. Incorporating information has become vital for risk stratification in cardiomyopathies, especially when myocardial inflammation is part of the clinical picture [182, 186].

5 | Therapeutic Perspectives in Inflammation Targeting

The recognition of myocardial inflammation in genetic cardiomyopathies has naturally led to attempts at targeted therapy beyond conventional heart failure and arrhythmia management. The goal of immunomodulatory therapy is to extinguish damaging inflammation, promote myocardial healing, and potentially alter the disease trajectory by delaying or preventing the onset of fibrosis and ventricular dysfunction. A future paradigm will likely involve combining gene- and immune-targeted strategies for maximal benefit. Inflammation may impact the efficacy of antiarrhythmic drugs. An inflamed myocardium exhibits altered drug receptor expression and impaired blood flow, which can potentially render arrhythmias more refractory to treatment. For instance, in active myocarditis, arrhythmias may respond poorly to class III antiarrhythmic agents until the underlying inflammation is adequately controlled. Reducing inflammation can thus be part of arrhythmia management, helping the heart respond better to medications or ablation procedures [7].

The main therapeutic strategies for myocardial inflammation in cardiomyopathies are represented in Figure 4.

5.1 | Conventional Immunosuppression

Corticosteroids and antimetabolites, including azathioprine or mycophenolate mofetil, have been used for decades in chronic myocarditis [201]. For example, in inflammatory cardiomyopathy, the TIMIC trial demonstrated that 6 months of prednisone plus azathioprine led to improvements in systolic function and functional status compared to placebo [116]. Conventional immunosuppression proved to be beneficial also on ventricular arrhythmias in active myocarditis [202, 203]. In patients with biopsy-proven myocarditis and likely-pathogenic/pathogenic variants in cardiomyopathy-associated genes, these regimens have shown benefit in case series [7]. Similarly, in *DSP*-cardiomyopathy with a myocarditis-like presentation, immunosuppressive drugs have been reported to reduce bursts of chest pain and ventricular arrhythmias, presumably by reducing myocardial edema [104]. These therapies are broad-acting, not targeting a specific pathway, but globally dampening the immune response to allow the heart to recover. The safety profile in cardiomyopathy patients appears acceptable, with the main caveat being to rule out active viral infection beforehand since immunosuppression can worsen a replicating viral myocarditis [4]. Immunosuppressive therapy in properly selected patients is safe and associated with LV reverse remodeling, and may also reduce arrhythmic events in these patients. Immunosuppressive therapy should also precede ventricular tachycardia ablation in patients with active myocardial inflammation and recurrent ventricular arrhythmias [204, 205].

5.2 | Cytokine-Targeted Therapies

Given the central role of certain cytokines in inflammatory heart damage, biologic drugs that neutralize these mediators have been piloted. The prime example is IL-1 blockade with anakinra, an IL-1 receptor antagonist [206]. Small studies and reports have shown that anakinra can lead to symptoms and systolic function improvement in myocarditis and inflammatory cardiomyopathy [207–209]. However, in the randomized ARAMIS trial, anakinra failed to demonstrate a

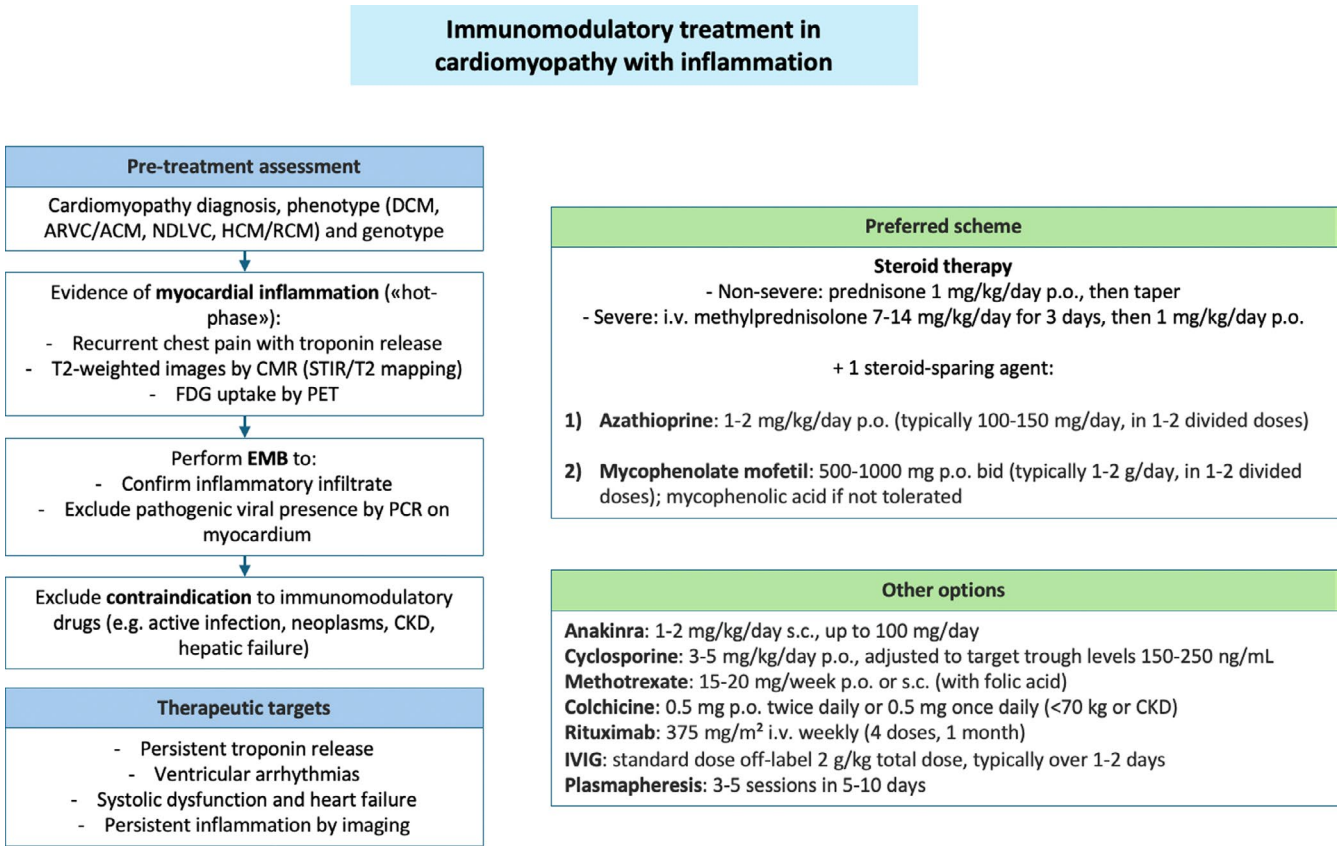

FIGURE 4 | Proposed therapeutic strategies for myocardial inflammation in genetic cardiomyopathies. The diagnostic assessment needed before starting immunomodulatory treatment in inflammatory cardiomyopathies is reported on the left. The main therapeutic schemes are summarized on the right. ACM, arrhythmogenic cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy; CKD, chronic kidney disease; DCM, dilated cardiomyopathy; EMB, endomyocardial biopsy; FDG, ^{18}F-fluorodeoxyglucose; HCM, hypertrophic cardiomyopathy; IVIG, intravenous immunoglobulin; NDLVC, non-dilated left ventricular cardiomyopathy; PCR, polymerase chain reaction; PET, positron emission tomography; RCM, restrictive cardiomyopathy; STIR, short-tau inversion recovery.

benefit in acute myocarditis, but showed its safety in patients with a cardiac magnetic resonance-proven diagnosis [210]. In the context of genetic cardiomyopathies, IL-1 inhibition has been used on a case-by-case basis in patients with recurrent inflammatory episodes, for example, recurrent myocarditis in *DSP* cardiomyopathy [7, 104]. Another cytokine target is IL-6. Tocilizumab, an anti-IL-6 receptor antibody, has been tried in some cases of myocarditis with anecdotal success in dampening hyperinflammation, though data remain limited [211, 212]. TNF-α is an attractive target in theory since TNF is elevated in heart failure and myocarditis, but trials of TNF-blockers like etanercept in chronic heart failure were disappointing in unselected patients and are not used routinely in cardiomyopathies [213].

Other immune pathways are being explored: for example, abatacept, a CTLA4-Ig that blocks T cell co-stimulation, is being studied in cardiac sarcoidosis and immune checkpoint inhibitor myocarditis [214]. This could have implications for treating granulomatous inflammation in *DSP*-cardiomyopathy that clinically mimics cardiac sarcoidosis [21]. Similarly, anti-B cell therapy like rituximab could be considered in cases where cardiac autoantibodies seem pathogenic, although this is not yet tested outside of small case series [215, 216].

5.3 | Pathway-Specific Interventions

Since NF-κB appears to be a final common pathway for inflammation in many genetic cardiomyopathies, drugs that inhibit NF-κB activation or related pathways are of great interest. Although direct NF-κB inhibitors are not clinically available because of off-target effects, certain existing drugs indirectly reduce NF-κB activity. For instance, colchicine, an anti-inflammatory drug used in pericarditis, has effects on the NLRP3 inflammasome and NF-κB pathways and is being tested in myocarditis and genetic cardiomyopathy patients [217, 218]. Standard anti-heart failure therapies also have anti-inflammatory properties: beta-blockers can reduce TNF-α levels, and ACE inhibitors/ARBs reduce leukocyte activation via angiotensin II inhibition [25]. These effects might partly explain why they improve outcomes in inflammatory cardiomyopathy as well.

In ACM models, inhibitors of the Wnt/β-catenin pathway have shown promise [56]. Some experimental or repurposed drugs that inhibit the Wnt pathway, such as tideglusib, could potentially slow ACM progression by mitigating both fibrosis and inflammation [219]. Also, NF-κB inhibitors have been used in preclinical ACM models successfully to halt disease progression by preventing fibrofatty changes and arrhythmias, although

such compounds are not yet clinically applicable [50]. Drugs that block CCR2+ monocytes trafficking could reduce macrophage-mediated damage in ACM [51]. Similar CCR2 antagonists are being trialed in other cardiac diseases and could be repurposed for myocarditis or genetic cardiomyopathies to prevent the influx of inflammatory macrophages [220].

5.4 | Treating Underlying Triggers

In cases where a virus or an autoimmune disease is identified as the trigger for myocardial inflammation, therapy directed at that cause is crucial. For example, if viral PCR from a biopsy is positive for a cardiotropic virus, antiviral therapies or high-dose IVIG can be considered. IVIG can neutralize viruses and modulate the immune response and has been used in fulminant myocarditis [221]. Trials with interferon-β in virus-positive inflammatory DCM showed clearance of viral genomes of enterovirus or adenovirus and some improvement in systolic function [222, 223]. For parvovirus B19, a common virus found in myocarditis biopsies, management is more contentious. Some centers try IVIG or interferon if high viral load is present; others consider parvovirus a bystander if only low-level DNA is detected, allowing immunosuppressive therapy [81, 224, 225]. If inflammation in a cardiomyopathy is related to a systemic autoimmune disease, then intensifying therapy for the autoimmune disease, such as high-dose steroids or cyclophosphamide for lupus myocarditis, becomes necessary [226]. Essentially, controlling the upstream cause, be it viral or autoimmune, is part of the immunotherapeutic approach in those scenarios and can lead to improvement in cardiac inflammation.

5.5 | Immunoadsorption and Tolerance Induction

In autoimmune-mediated cardiomyopathy with evidence of autoantibodies against cardiac antigens, strategies like immunoadsorption, which is a form of plasmapheresis to remove antibodies, followed by intravenous immunoglobulin (IVIG) have been employed. Some trials showed that DCM patients undergoing immunoadsorption had improvements in cardiac function and reductions in myocardial autoantibody levels [227]. This approach essentially resets the humoral immune profile by clearing pathogenic antibodies and then modulating the immune system with IVIG. Another concept is the induction of immune tolerance: for instance, using peptides or altered antigens to retrain the immune system not to attack cardiac proteins. However, this is hypothetical at this point for myocarditis/DCM, but analogous strategies are used in other autoimmune diseases.

5.6 | ICD Implantation and Arrhythmia Catheter Ablation

Another aspect where inflammation intersects with arrhythmic risk is in device therapy decision-making [1]. If a patient has active myocarditis, it might be reasonable to temporize before committing to an ICD or to use a Life-Vest because the arrhythmic risk may be transient and tied to inflammation. In other words, some patients who meet standard ICD criteria on the basis of systolic function or arrhythmias could improve once the inflammation is treated, and thus an ICD might become unnecessary in the long term. This concept is still developing and requires careful clinical judgment and prospective validation. Catheter ablation during the active phase of myocarditis is not warranted, except in uncontrolled electrical storm, since it is associated with more recurrence than when performed after inflammation resolution [205]. This finding aligns with the principle of "cool down, then ablate", which stands for prioritizing immunomodulatory therapy to reduce inflammation-related arrhythmias, and then performing ablation of residual scar-related ones [204].

In summary, therapy for genetic cardiomyopathies is evolving from a "one-size-fits-all" approach to a tailored strategy addressing both the genetic substrate and the immune component. The guiding principle is to treat the cause, not just the effect: suppress the immune attack if present, and in time, fix or compensate for the genetic error. This comprehensive approach promises not only to improve outcomes but to also fundamentally alter disease courses, potentially converting what might have been a progressive, debilitating illness into a manageable or even reversible condition. The future likely lies in combination therapy addressing both the genetic and immune aspects.

6 | Conclusions

Inflammation is a fundamental dimension of primary genetic cardiomyopathies, influencing their clinical expression, progression, and outcomes. Far from being separate entities, genetic variants and immune-mediated injury often act in concert to cause myocardial damage.

Research into inflammation and immunogenetics in cardiomyopathy is rapidly advancing. We now appreciate that pathways like NF-κB and T cell activation can be directly or indirectly triggered by genetic variants in heart muscle cells. The concept of the "final common pathway" in heart failure and arrhythmias is being expanded to include immune pathways converging with mechanical and electrical pathways. The clinical takeaway is that therapy needs to be broadened: in addition to conventional antiarrhythmic and anti-remodeling treatments, appropriate patients may benefit from immunosuppression and from emerging gene-specific interventions.

Future directions will likely involve routine integration of immunological profiling, such as circulating cytokines and autoantibodies, in cardiomyopathy evaluations. This combined approach could stratify patients into more precise categories: those who might spontaneously improve, those who need immunomodulatory therapy, and those who need early referral for advanced management. Clinical trials are needed to formally test immunosuppressive therapy in gene-positive inflammatory cardiomyopathy, as well as to test anti-cytokine drugs in this setting. On the genetic side, trials of gene therapies and RNA-based therapies are eagerly anticipated.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

This is a review article with no original data.

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