Review

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Review

From Inflammation to Inheritance: Rethinking Myocarditis as the First Signal of Desmosomal Cardiomyopathy

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Abstract

Acute myocarditis has traditionally been regarded as an acquired inflammatory disorder of the myocardium, most commonly triggered by viral infection or immune-mediated injury. However, growing evidence suggests that in a subset of patients, myocarditis may represent the initial clinical manifestation of an underlying genetic cardiomyopathy rather than a purely inflammatory disease. Recent advances in molecular genetics, cardiac magnetic resonance imaging, and translational pathology have revealed a significant overlap between myocarditis and inherited cardiomyopathies, particularly those related to desmosomal dysfunction. Desmosomal gene variants—most frequently involving desmoplakin, plakophilin-2, and desmoglein-2—have been increasingly identified in patients presenting with myocarditis-like syndromes characterized by chest pain, troponin elevation, and imaging findings fulfilling Lake Louise criteria. Importantly, these presentations often demonstrate recurrent inflammatory episodes, ventricular arrhythmias, and progressive myocardial fibrosis that ultimately evolve into the structural phenotype of arrhythmogenic cardiomyopathy. Emerging mechanistic data further suggest that structural instability of the intercalated disc may trigger autoimmune responses through exposure of desmosomal antigens and generation of disease-specific autoantibodies such as anti-DSG2. This review explores the evolving concept of myocarditis as an inflammatory manifestation of genetically mediated cardiomyopathy and highlights the diagnostic and mechanistic implications of this gene–immune interaction.

Keywords: acute myocarditis; desmosomes; recurrent myocarditis; hot phase

Background

Acute myocarditis has traditionally been regarded as an acquired inflammatory disease of the myocardium, most commonly triggered by viral infection or immune-mediated mechanisms, with outcomes ranging from complete recovery to chronic dilated cardiomyopathy [1]. However, growing evidence suggests that this classical dichotomy between "inflammatory" and "genetic" myocardial disease is increasingly artificial. In recent years, advances in cardiac imaging, molecular pathology, and genetic testing have revealed a substantial overlap between myocarditis and inherited cardiomyopathies, particularly arrhythmogenic and dilated phenotypes [2]. Clinically, this overlap is frequently manifested by myocarditis-like presentations characterized by chest pain, troponin

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elevation, electrocardiographic changes, and cardiac magnetic resonance (CMR) features fulfilling Lake Louise criteria, yet followed by recurrent inflammatory episodes, malignant arrhythmias, or progressive myocardial dysfunction disproportionate to the apparent inflammatory burden. These observations have prompted a paradigm shift in which myocarditis is no longer viewed solely as an isolated inflammatory insult, but rather, in a subset of patients, as the initial clinical expression of a genetically determined myocardial disease [3].

Figure 1. Graphical abstract: Hypothesis of myocarditis-hot phase of desmosomal related cardiomyopathies.

Recent translational and clinical studies strongly support this concept by demonstrating a high prevalence of pathogenic or likely pathogenic variants in cardiomyopathy-related genes among patients presenting with myocarditis or inflammatory cardiomyopathy. In particular, desmosomal gene variants—classically associated with arrhythmogenic cardiomyopathy—have emerged as a dominant genetic substrate in these patients. In a landmark multimodal imaging and biopsy-based study, Peretto and colleagues showed that nearly half of patients with biopsy-proven myocardial inflammation carried desmosomal mutations, most commonly involving desmoplakin, and uniformly presented with myocarditis-like episodes marked by chest pain and ventricular arrhythmias [4].

Importantly, these patients demonstrated extensive replacement fibrosis with relatively limited necrosis, suggesting that inflammation may act as a disease modifier rather than the primary driver of myocardial injury. Complementing these findings, a large genetic screening study of patients with suspected myocarditis identified pathogenic variants in approximately one-quarter of cases, with a significant proportion involving genes associated with arrhythmogenic and dilated cardiomyopathies, including desmoplakin, lamin A/C [5].

Accordingly, this article explores the emerging hypotheses that seek to explain why certain genetic cardiomyopathies—particularly those involving desmosomal dysfunction—may clinically manifest as recurrent myocarditis-like episodes, positioning inflammation as a key modifier of an underlying inherited myocardial substrate.

Main Body

Myocarditis-Like Episodes in Desmosomal Cardiomyopathies

Accumulating evidence suggests that a subset of patients presenting with acute myocarditis may harbor an underlying genetic cardiomyopathy, particularly those associated with pathogenic variants in desmosomal proteins. Desmosomal cardiomyopathies, traditionally grouped under arrhythmogenic cardiomyopathy (ACM), are inherited myocardial disorders characterized by ventricular arrhythmias, myocardial fibrosis, and progressive ventricular dysfunction. However, contemporary data indicate that inflammatory myocardial injury is an important component of disease pathophysiology and may represent one of the earliest clinical manifestations of desmosomal disease. In this context, acute myocarditis-like presentations may precede the overt structural phenotype of arrhythmogenic cardiomyopathy and may occur repeatedly over time [6,7].

Desmosomes are essential intercellular junctions that provide mechanical coupling between cardiomyocytes within the intercalated disc. They are composed of multiple structural proteins including desmoplakin (*DSP*), plakophilin-2 (*PKP2*), desmoglein-2 (*DSG2*), and desmocollin-2 (*DSC2*). Mutations in these genes disrupt cardiomyocyte adhesion and increase susceptibility to mechanical stress and injury. As a consequence, myocardial cell death may occur, triggering inflammatory responses that clinically mimic acute myocarditis. Genetic variants affecting these structural proteins have increasingly been identified in patients presenting with myocarditis without an obvious infectious etiology, suggesting that myocarditis may represent an inflammatory manifestation of an underlying structural cardiomyopathy [3,8].

One of the largest studies examining this association was the international registry reported by Ammirati and colleagues, which evaluated patients presenting with acute myocarditis in the

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presence of desmosomal gene variants. In this cohort, the majority of identified variants involved the *desmoplakin* gene, highlighting its prominent role in inflammatory cardiomyopathy phenotypes. Patients typically presented with classical symptoms of acute myocarditis including chest pain and troponin elevation, while ventricular systolic function was often preserved at presentation. Importantly, patients with desmosomal gene variants experienced a markedly higher rate of adverse cardiovascular events compared with patients with myocarditis without such variants, particularly driven by recurrent myocarditis episodes and ventricular arrhythmias during follow-up. These findings strongly suggest that myocarditis in the setting of desmosomal disease represents an early stage of the underlying cardiomyopathy rather than an isolated inflammatory event [9].

Recurrent myocarditis has therefore emerged as a key clinical clue pointing toward a genetic arrhythmogenic cardiomyopathy. This concept was further supported by a longitudinal study examining patients with recurrent acute myocarditis without previously known cardiomyopathy. During follow-up, a large proportion of these patients subsequently developed phenotypic features consistent with arrhythmogenic cardiomyopathy. Genetic testing revealed pathogenic variants in several cardiomyopathy-related genes, most frequently involving desmosomal proteins such as *desmoplakin* and *plakophilin-2*. Importantly, these inflammatory episodes often preceded the structural manifestations of cardiomyopathy by several years, suggesting that recurrent myocarditis represents an early inflammatory phase of the disease process. The authors proposed that recurrent myocarditis episodes should be considered an under-recognized manifestation of arrhythmogenic cardiomyopathy and potentially incorporated into future diagnostic frameworks for the disease [10].

Among the various desmosomal genes, *desmoplakin* mutations appear particularly associated with inflammatory myocardial injury and recurrent myocarditis. Poller and colleagues described a striking familial phenotype involving recurrent myocarditis in two brothers carrying a truncating variant of the *DSP* gene. Both patients experienced repeated episodes of chest pain accompanied by significant troponin elevation and electrocardiographic changes consistent with acute myocarditis. Cardiac magnetic resonance imaging demonstrated multifocal subepicardial late gadolinium enhancement involving the left ventricle, a pattern frequently observed in myocarditis-like presentations. Extensive virological testing failed to identify infectious triggers, suggesting that myocardial inflammation resulted from intrinsic structural vulnerability of the myocardium rather than viral injury. These observations support the concept that desmosomal dysfunction may lead to mechanical instability of cardiomyocytes, promoting myocardial injury and secondary inflammatory responses that manifest clinically as recurrent myocarditis [11].

Autoimmune Mechanisms Linking Desmosomal Mutations to Myocarditis-Like Injury

One of the proposed mechanisms linking desmosomal mutations to inflammatory myocardial injury involves an autoimmune cascade triggered by structural instability of the cardiomyocyte intercalated disc. Desmosomes are critical mechanical junctions that anchor cardiomyocytes together and maintain myocardial structural integrity during repetitive contraction. These junctions are composed of several structural proteins, including desmoplakin (DSP), plakophilin-2 (PKP2), desmoglein-2 (DSG2), and desmocollin-2 (DSC2). Mutations affecting these proteins disrupt cell–cell adhesion and compromise the mechanical stability of the intercalated disc. As a result, cardiomyocytes become more vulnerable to mechanical stress and injury, particularly during increased hemodynamic load or physical activity [12–14].

Structural disruption of the desmosomal complex may promote **cellular injury and desmosomal protein shedding**, leading to the release of intracellular or junctional antigens into the extracellular environment. Under physiological conditions, many of these proteins remain sequestered within intercellular junctions and are not exposed to the immune system. However, desmosomal dysfunction may expose previously concealed epitopes, allowing them to be recognized as neoantigens by antigen-presenting cells. This process may trigger an adaptive immune response

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involving activation of T cells and B cells, ultimately resulting in the generation of autoantibodies directed against desmosomal proteins [15,16].

Among these autoantibodies, antibodies targeting desmoglein-2 (DSG2) have received particular attention. Studies have demonstrated that anti-DSG2 autoantibodies can be detected in a high proportion of patients with arrhythmogenic cardiomyopathy and appear to be highly specific for the disease phenotype. In a landmark investigation, Chatterjee and colleagues identified circulating anti-DSG2 antibodies in essentially all individuals fulfilling diagnostic criteria for arrhythmogenic right ventricular cardiomyopathy, while these antibodies were absent in control populations and in patients with other cardiomyopathies [17–19].

The presence of these antibodies suggests that autoimmunity may play a central role in the pathogenesis of desmosomal cardiomyopathy rather than being merely a secondary epiphenomenon [18].

Experimental studies further support a functional role for these autoantibodies in disease progression. Anti-DSG2 antibodies have been shown to interfere with normal intercellular junctional signaling and impair electrical coupling between cardiomyocytes. Specifically, these antibodies appear capable of disrupting connexin-43 mediated gap-junction communication, a well-recognized hallmark of arrhythmogenic cardiomyopathy. Impaired electrical coupling may contribute to conduction abnormalities and ventricular arrhythmias, which often represent the earliest clinical manifestations of the disease. Moreover, antibody-mediated disruption of desmosomal and gap-junctional integrity may exacerbate mechanical instability within the myocardium, thereby amplifying cellular injury and perpetuating a cycle of inflammation and structural remodeling [11,17].

Once generated, these autoantibodies may perpetuate myocardial injury through several immune-mediated mechanisms. Binding of antibodies to desmosomal targets on cardiomyocytes may activate complement pathways or recruit inflammatory cells such as macrophages and lymphocytes. The resulting inflammatory cascade can lead to focal myocardial necrosis, producing clinical episodes that resemble acute myocarditis. These inflammatory flares may correspond to the so-called **“hot phases”** described in patients with arrhythmogenic cardiomyopathy, characterized by chest pain, troponin elevation, and cardiac magnetic resonance imaging findings suggestive of myocarditis [20].

Importantly, these myocarditis-like episodes often occur **recurrently**, which distinguishes them from typical viral myocarditis. Recurrent inflammatory injury may reflect repeated activation of autoimmune mechanisms rather than reinfection with viral pathogens. In this context, the inflammatory episodes may represent transient exacerbations of an underlying genetically mediated cardiomyopathy rather than isolated inflammatory disease. Over time, repeated cycles of immune-mediated myocardial injury lead to progressive replacement of healthy myocardium with fibrotic or fibro-fatty tissue [21].

The accumulation of fibrosis and scar tissue disrupts both mechanical and electrical myocardial function. Progressive structural remodeling ultimately results in ventricular dysfunction, chamber dilation, and an increased susceptibility to malignant ventricular arrhythmias. These pathological changes constitute the classical phenotype of arrhythmogenic cardiomyopathy. Thus, the autoimmune cascade triggered by desmosomal dysfunction may provide a mechanistic bridge linking early inflammatory manifestations to the later structural stages of the disease [22].

This autoimmune model also helps explain several observations frequently reported in desmosomal cardiomyopathy. Histological examination of myocardial specimens often reveals lymphocytic infiltrates, suggesting active immune involvement. Additionally, patients frequently present with myocarditis-like symptoms early in the disease course before overt ventricular remodeling becomes apparent. The presence of circulating anti-desmosomal antibodies may therefore represent both a biomarker of disease and a potential mediator of myocardial injury [23].

Taken together, these findings support the concept that desmosomal cardiomyopathies may involve a **gene–immune interaction**, in which structural defects in intercellular junctions initiate

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autoimmune responses that amplify myocardial damage. In this framework, recurrent myocarditis-like episodes may represent a hallmark of early disease activity and could serve as an important clinical clue suggesting the presence of an underlying desmosomal cardiomyopathy.

Conclusion

The emerging intersection between myocarditis and inherited cardiomyopathies challenges the traditional view that myocardial inflammation represents an isolated acquired disorder. Increasing clinical and genetic evidence indicates that in a substantial proportion of patients, myocarditis-like presentations may represent an early manifestation of underlying desmosomal cardiomyopathy. Recurrent inflammatory episodes characterized by chest pain, troponin elevation, and cardiac magnetic resonance findings consistent with myocarditis may therefore reflect transient inflammatory "hot phases" of a genetically mediated myocardial disease rather than recurrent viral injury. Mutations affecting desmosomal proteins disrupt cardiomyocyte adhesion and mechanical stability, predisposing the myocardium to injury and inflammatory activation. Furthermore, emerging data support a potential autoimmune component in which exposure of desmosomal epitopes leads to the generation of pathogenic autoantibodies such as anti-desmoglein-2, which may contribute to electrical uncoupling, myocardial inflammation, and progressive structural remodeling. Over time, repeated cycles of inflammatory injury may culminate in replacement fibrosis, ventricular dysfunction, and the classical arrhythmogenic cardiomyopathy phenotype. Recognition of this gene–inflammation interaction has important clinical implications, particularly in patients presenting with recurrent myocarditis. Early genetic testing, advanced imaging, and careful arrhythmic risk assessment may allow earlier diagnosis and improved risk stratification in this evolving disease paradigm.

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List of Abbreviations

Abbreviation	Full Term
ACM	Arrhythmogenic Cardiomyopathy
ARVC	Arrhythmogenic Right Ventricular Cardiomyopathy
CMR	Cardiac Magnetic Resonance
CM	Cardiomyopathy
DSP	Desmoplakin
DSG2	Desmoglein-2
DSC2	Desmocollin-2

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PKP2	Plakophilin-2
LGE	Late Gadolinium Enhancement
LV	Left Ventricle
RV	Right Ventricle
EDP	End-Diastolic Pressure
ECG	Electrocardiogram
EMB	Endomyocardial Biopsy
NF-κB	Nuclear Factor Kappa-B
Anti-DSG2	Anti-Desmoglein-2 Autoantibodies

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