American Journal of Medicine and Medical Sciences 2025, 15(8): 2706-2712
DOI: 10.5923/j.ajmms.20251508.60

Immune Aspects of the Pathogenesis of Dilated Cardiomyopathy

Rakhmatullaev A. A.[1,*], Saidov M. A.[1], Ziyadullaev Sh. Kh.[1], Khatamov Kh. M.[1], Ibragimov Kh. I.[2]

[1]Institute of Immunology and Human Genomics, Academy of Sciences of the Republic of Uzbekistan, National Medical Center
[2]Samarkand State Medical University, Samarkand, Uzbekistan

Abstract Dilated cardiomyopathy (DCM) is a progressive myocardial disorder of multifactorial origin, marked by ventricular dilatation and impaired systolic function. While genetic mutations in sarcomeric and cytoskeletal proteins underlie a subset of familial DCM, increasing evidence implicates immune-mediated mechanisms-often triggered by viral myocarditis, molecular mimicry, and persistent autoimmunity-in both idiopathic and post-infectious forms. This review synthesizes recent insights into the innate and adaptive immune responses that drive chronic myocardial inflammation and remodeling in DCM. Pattern recognition receptors (e.g., TLRs), proinflammatory cytokines (e.g., TNF-α, IL-6), and autoreactive T and B cells contribute to progressive cardiomyocyte damage. Autoantibodies against β_1-adrenergic and muscarinic receptors further perpetuate dysfunction. Endomyocardial biopsies, cytokine profiling, and next-generation sequencing are instrumental for immunophenotyping and identifying genetic/epigenetic predispositions. We discuss the application of immunosuppressants, IVIG, cytokine blockers, and immunoadsorption, alongside the promise of stratified medicine. Single-cell transcriptomics and flow cytometry now enable patient-specific treatment targeting pathways such as Th17 polarization, B-cell activation, or cytokine dysregulation. Moreover, the integration of epigenetic biomarkers-DNA methylation, histone modifications, and miRNAs-offers predictive and therapeutic insights. In conclusion, DCM exemplifies the intersection of immunology and cardiology, where precision immunotherapy tailored to individual immune profiles may enhance therapeutic efficacy, reduce adverse outcomes, and redefine disease management paradigms.

Keywords Dilated cardiomyopathy, Autoimmunity, Viral myocarditis, Immunotherapy, Precision medicine

1. Introduction

Cardiomyopathies represent a heterogeneous group of disorders characterized by impaired mechanical and/or electrical function of the myocardium, leading to dilated, hypertrophic, or restrictive forms of pathophysiology. Dilated cardiomyopathy (DCM) can be caused by genetic mutations, infections, inflammation, autoimmune diseases, toxic exposures, as well as endocrine or neuromuscular conditions [1]. The most common etiologies are idiopathic and familial forms. Advances in genetic sequencing and molecular technologies have enhanced clinicians' ability to determine the underlying etiology and provide personalized risk stratification [2]. Clinical heterogeneity, including variations in sex, age, progression rate, risk of heart failure, and sudden cardiac death, further complicate the natural course of the disease. The prevalence of idiopathic DCM was historically estimated at approximately 1:2,500 in a population-based study conducted in Minnesota between 1975 and 1984 [3,4]. However, more recent data suggest a higher prevalence-about 1:250 in developed countries and closer to 1:400 in developing regions, based on heart failure diagnoses [5].

It is important to emphasize that in both primary and secondary DCM, the immune system plays an integral role not only in the pathogenesis but also as a target for potential therapeutic interventions. Inflammatory cardiomyopathies-commonly of viral, autoimmune, or idiopathic origin-often exhibit persistent immune activation long after the initial insult. This immune dysregulation contributes to progressive myocyte injury, ventricular remodeling, and impaired systolic function. Several lines of evidence indicate that both innate and adaptive immune responses are involved in this pathological cascade. Innate immunity is activated through pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs), leading to the release of proinflammatory cytokines, while adaptive immunity contributes via T- and B-cell-mediated responses, including the formation of cardiotropic autoantibodies.

Furthermore, recent studies have revealed that immune-mediated mechanisms-particularly viral persistence, molecular mimicry, and the production of cardiac autoantibodies-are central to the progression from acute myocarditis to

* Corresponding author:
res.ssmu@gmail.com (Rakhmatullaev A. A.)
Received: Aug. 4, 2025; Accepted: Aug. 22, 2025; Published: Aug. 26, 2025
Published online at http://journal.sapub.org/ajmms

chronic DCM. For example, antibodies directed against β_1-adrenergic receptors, cardiac myosin, and mitochondrial antigens have been associated with worse clinical outcomes and ventricular dysfunction. Understanding these immunopathological mechanisms has led to the exploration of immunomodulatory and immunosuppressive therapies, including corticosteroids, intravenous immunoglobulin (IVIG), and B-cell depletion strategies. However, clinical trials have shown mixed results, highlighting the need for better patient stratification and biomarker-guided approaches.

This review aims to critically analyze recent insights into the immunological mechanisms involved in the pathogenesis of DCM and to discuss their implications for diagnosis, prognosis, and targeted therapy.

2. Materials and Methods

Literature Review

A comprehensive literature review was conducted to examine immunological mechanisms contributing to the pathogenesis of dilated cardiomyopathy (DCM), with particular emphasis on cytokine polymorphisms, immune cell activation, and inflammation-related myocardial remodeling. The aim was to synthesize findings regarding immune dysregulation as both a trigger and perpetuator of myocardial dysfunction. Literature searches were performed in the PubMed, Scopus, Web of Science, and Google Scholar databases. The following keywords and Boolean combinations were used: "dilated cardiomyopathy" AND ("immune response" OR "cytokines" OR "T cells" OR "NK cells" OR "TNF-alpha" OR "IL-6" OR "autoimmunity" OR "myocarditis" OR "immunopathology" OR "cardiac inflammation"). Studies were filtered for relevance to human immunology and cardiac structural outcomes.

Inclusion and Exclusion Criteria

Inclusion criteria encompassed peer-reviewed original research articles, systematic reviews, and meta-analyses published in English from 2000 to 2025. Studies were included if they fulfilled at least one of the following:

- reported immunological alterations in patients with idiopathic or secondary DCM,
- analyzed cytokine or immune gene polymorphisms associated with disease progression,
- described mechanisms of autoimmune or virus-induced myocardial inflammation,
- proposed or evaluated immunomodulatory therapies in DCM.

Exclusion criteria were:

- non-human or purely in vitro studies unless directly relevant to clinical mechanisms,
- case reports without immunological or diagnostic validation,
- editorials or non-peer-reviewed opinions,
- non-English studies without translated versions.

Data Extraction

Data extraction was structured to capture key aspects of immune-related findings in DCM, including:

- Peripheral and myocardial immune cell phenotyping (e.g., CD4+, CD8+ T cells, NK cells, macrophages)
- Circulating cytokine levels (e.g., TNF-α, IL-6, IL-10) and gene polymorphisms (e.g., TNFA -308G/A, IL10 -1082G/A)
- Evidence of autoimmune reactivity (e.g., autoantibodies, T-cell infiltration)
- Role of infection-triggered inflammation (e.g., viral myocarditis)
- Outcomes from studies evaluating immunosuppressive or biologic therapies
- Clinical endpoints such as ejection fraction, ventricular dilation, and symptom progression

Studies were categorized thematically into: mechanistic immunopathology, genetic immunology, and immune-targeted therapies.

Analysis

Thematic synthesis was applied to identify immune-related patterns across diverse DCM etiologies. Emphasis was placed on chronic immune activation markers, polymorphism -associated immune phenotypes, and inflammatory cytokine profiles predictive of disease severity or therapeutic response. Studies on idiopathic, post-viral, and autoimmune DCM were analyzed separately to preserve etiology-specific immune mechanisms. Findings were integrated into a conceptual model of immune-mediated cardiac remodeling and dilatation.

Ethical Considerations

This review was conducted using only publicly available, previously published data. No new clinical data were collected, and ethical approval was not applicable. All included studies adhered to ethical publication standards and are cited accordingly.

Limitations

This review is limited by heterogeneity in diagnostic criteria, immune marker measurement techniques, and patient populations across studies. Variation in methods of cytokine quantification, genotyping, and immunophenotyping complicates direct comparisons. Additionally, many studies included small sample sizes or lacked long-term follow-up. Future research integrating systems immunology, cardiac imaging, and multicenter cohorts is necessary to validate proposed immune mechanisms and identify therapeutic targets in DCM.

3. Results

Etiopathogenesis of Dilated Cardiomyopathy: The Role of Immunological Mechanisms

Dilated cardiomyopathy (DCM) is a genetically determined

disease resulting from mutations in genes encoding structural proteins of the sarcomere and desmosomes. The hereditary form accounts for approximately 20–30% of cases, highlighting the significant contribution of genetic factors. Over 50 genes have been implicated in DCM, with 12 playing key roles in its development. Truncating variants in the TTN gene, which encodes titin (the largest sarcomeric protein), are the most frequent mutations linked to familial DCM, found in approximately 25% of cases [6]. Family aggregation studies support this: in one cohort of first-degree relatives of DCM patients (n=342), 20% of asymptomatic relatives tested positive for cardiac autoantibodies, compared to only 3.5% in controls (p=0.0001). Those positive relatives also showed early echocardiographic changes, such as increased LV end-systolic diameter and reduced fractional shortening [7].

Injury to the myocardium from infections, autoimmune conditions, pharmaceuticals, or environmental toxins initiates inflammatory responses that lead to left ventricular (LV) dysfunction and dilation. Even in non-infectious myocarditis, progression to DCM is common [2]. Cardiotoxic agents -including alcohol, chloroquine, psychotropic medications, and some chemotherapy drugs-can severely impair myocardial function and lead to DCM.

Viral myocarditis is a major cause of DCM, commonly caused by Coxsackie B3 virus, parvovirus B19, and human herpesvirus 6 (HHV-6) [8]. Coxsackie B3 is the prototype of endemic myocarditis, responsible for most biopsy-proven cases [9]. Parvovirus B19 infects erythroid progenitor and cardiac endothelial cells, leading to microvascular inflammation and cytokine release (IL-6, TNF-α), contributing to myocardial damage [10]. HHV-6 is lymphotropic and integrates into the host genome, which complicates the interpretation of chromosomally integrated forms in patients with myocardial involvement [11].

Viral myocarditis typically evolves through acute, subacute, and chronic stages. Molecular diagnostics reveal viral genomes in 60–70% of inflammatory cardiomyopathy cases [12]. Persistent viral genomes correlate with worse clinical outcomes, including reduced LV ejection fraction, increased arrhythmia risk, and progression to DCM [13,14]. Molecular mimicry is a key immunological mechanism by which viruses trigger autoimmunity. For example, Coxsackie B3 VP1 and VP2 capsid proteins share peptide motifs with cardiac myosin and troponin. T cells activated by viral antigens may cross-react with myocardial antigens, initiating autoimmune myocarditis [15–17]. Similarly, B19 infection can expose hidden myocardial antigens through viral cytotoxicity, perpetuating inflammation even after viral clearance [18]. Anti-idiotypic antibody formation is another proposed mechanism where antibodies against viral antigens mimic cardioreceptor structures, exacerbating autoimmunity.

Understanding virus-host interactions-including receptor tropism (e.g., CAR), host protein cleavage by viral proteases, and mimicry-induced autoimmunity-is critical for new treatments. For instance, CAR-Fc soluble receptors have shown promise in blocking CVB3 entry. Peptide-based tolerance strategies using mimetic antigens are also being tested in animal models [19].

In essence, viral myocarditis from CVB3, B19, or HHV-6 can initiate a cascade of innate and adaptive immune responses. If viruses are cleared effectively, recovery is possible. If not, molecular mimicry and autoimmunity may lead to chronic inflammation and DCM.

Autoimmune cascades involve circulating autoantibodies, particularly against β_1-adrenergic receptors (β_1AR), and dysregulated T-cell subsets (Th1, Th17, $CD8^+$ cytotoxic T cells) [20]. β_1AR autoantibodies are present in 26–60% of idiopathic DCM cases and correlate with poor outcomes: reduced ejection fraction, arrhythmias, and higher mortality [21]. Other autoantibodies target M_2 muscarinic receptors, cardiac myosin, troponin I, ANT, and mitochondrial proteins-found in >40% of non-ischemic DCM cases [22].

B cells contribute to DCM not only by producing autoantibodies but also by presenting antigens and secreting cytokines. β_1AR autoantibodies act as functional agonists, inducing chronic signaling, receptor desensitization, impaired internalization, calcium overload, apoptosis, and arrhythmogenesis [23]. Th1- and Th17-type $CD4^+$ T cells amplify myocardial inflammation and promote the chronic transition to DCM through IFN-γ and IL-17A release, respectively [24]. $CD8^+$ cytotoxic T cells mediate direct cardiomyocyte lysis via perforin, granzymes, and FasL, particularly in virus-triggered autoimmunity.

T–B cell interactions, including IL-6–driven Th17 differentiation and the recruitment of tertiary lymphoid aggregates rich in B cells, maintain the autoimmune loop. β_1AR autoantibodies triple cardiovascular mortality risk independently of LVEF, NYHA class, or arrhythmia burden [25,26].

The innate immune response is initiated by cardiac macrophages, endothelial cells, and fibroblasts expressing pattern recognition receptors (PRRs). Upon myocardial damage, these cells recognize pathogen- or danger-associated molecular patterns (PAMPs, DAMPs) via TLRs (e.g., TLR3, TLR7), triggering release of proinflammatory cytokines: TNF-α, IL-1β, and IL-6 [27-30]. These promote leukocyte infiltration, vascular permeability, and a proinflammatory cardiac environment [31-33].

Adaptive immunity, characterized by antigen-specific clonal expansion, becomes maladaptive in DCM. Th1 and Th17 $CD4^+$ cells secrete IFN-γ and IL-17A, while $CD8^+$ T cells cause mesenchymal cell lysis via perforin, granzymes, or Fas [34,35]. Regulatory T cells are often deficient or dysfunctional in autoimmune cardiomyopathy, failing to suppress autoreactive clones [36].

B cells, in addition to antigen presentation and cytokine release, produce pathogenic autoantibodies against β_1AR, M_2R, myosin, troponin I, Na^+/K^+ ATPase, and mitochondrial proteins [37,38]. These antibodies act as receptor agonists/ antagonists, disrupt intracellular signaling, activate complement cascades, and form immune complexes that deposit in myocardium, promoting chronic inflammation and structural remodeling [39].

Both innate and adaptive responses-though initially protective-become pathologic with chronic activation, loss of tolerance, and persistent inflammation. A deeper understanding of these processes informs diagnostics and opens avenues for immunotherapeutic interventions.

Dendritic cells (DCs), though scarce, act as key antigen-presenting cells. Upon TLR activation, DCs migrate to lymphoid tissues and present viral or self-antigens to naïve T cells, promoting Th1 and Th17 responses that extend inflammation beyond acute infection. They also release IL-12, IL-23, and type I interferons, shaping downstream immunity. These cytokines expand autoreactive T cells and drive the transition from viral myocarditis to autoimmune DCM [40].

Cytokine storm-marked by TNF-α, IL-6, and IL-1β release-is a hallmark of severe cardiac inflammation. TNF-α disrupts calcium handling, induces nitric oxide production, promotes apoptosis, and enhances endothelial adhesion molecule expression. Elevated TNF-α correlates with poor prognosis in heart failure [41]. IL-6 activates STAT3, triggering fibroblast activation, collagen synthesis, and LV remodeling [42]. IL-1β enhances leukocyte recruitment and endothelial activation, worsening cardiac repair microenvironments [43]. Chemokines like CCL2 and CXCL10 attract monocytes and T cells, perpetuating myocardial inflammation [44].

Diagnosis and Treatment

When dealing with immune-mediated diseases, particularly those affecting the heart, establishing an accurate diagnosis and initiating effective therapy require several key steps. The diagnostic process begins with the assessment of immune system activation biomarkers in peripheral blood. This includes measuring circulating cytokine levels-signaling molecules that mediate inflammation-and identifying disease-specific autoantibodies that mistakenly target the body's own tissues, including cardiac structures. These markers are instrumental not only in diagnosing immune activation but also in monitoring disease activity over time [45,46].

However, for a definitive diagnosis-especially when myocarditis or autoimmune cardiomyopathy is suspected-more direct tissue analysis is often necessary. Endomyocardial biopsy plays a central role in such cases, allowing direct histological evaluation of myocardial samples. This procedure is complemented by immunohistochemical analysis, which identifies infiltrating immune cells (e.g., T cells, macrophages) and tissue-bound immune mediators, offering critical insight into the cellular and molecular landscape of the myocardial lesion [47]. Additionally, advanced molecular techniques such as PCR-based viral genome detection and RNA sequencing can further differentiate between viral persistence, autoimmune activation, and sterile inflammation, thereby refining diagnostic accuracy and guiding treatment choices [47].

Following diagnosis, the primary therapeutic goal is immunomodulation. Immunosuppressive therapy constitutes the cornerstone of treatment. Corticosteroids are frequently employed due to their broad anti-inflammatory and immunosuppressive effects. They downregulate the production of proinflammatory cytokines, inhibit lymphocyte activation, and reduce myocardial infiltration. In severe or refractory cases, intravenous immunoglobulin (IVIG) may be administered, exerting multifaceted immunoregulatory actions including Fc receptor blockade, anti-idiotypic antibody formation, and inhibition of complement-mediated cytotoxicity. Another advanced option includes immunoadsorption therapy, which selectively removes pathogenic autoantibodies or circulating immune complexes from the bloodstream, often leading to improvements in left ventricular ejection fraction and symptom burden [48].

Beyond general immunosuppression, targeting specific immune pathways is becoming increasingly feasible. Looking ahead, the field is rapidly evolving with the development of targeted biologic therapies. These include monoclonal antibodies specifically designed to neutralize proinflammatory cytokines such as TNF-α, IL-6, and IL-1β, or to modulate immune checkpoints that govern T-cell activation. Early-phase clinical studies suggest these agents can reduce inflammation, prevent myocardial remodeling, and delay the progression to end-stage heart failure in select populations. Furthermore, cell-based therapies-such as regulatory T-cell (Treg) infusions or tolerogenic dendritic cells-are under investigation for their ability to restore immune tolerance and promote myocardial repair. These cellular interventions aim to reestablish immunologic homeostasis by suppressing autoreactive lymphocytes and promoting anti-inflammatory cytokine environments [49].

In parallel, the concept of personalized immunotherapy is gaining momentum, emphasizing treatment stratification based on the patient's unique immunologic and genetic profile. This includes HLA haplotyping, cytokine gene polymorphism analysis, and autoantibody profiling to guide drug selection and dosage optimization. Emerging data also support the use of multi-omics platforms-including transcriptomics, proteomics, and single-cell immunophenotyping-to identify novel biomarkers for early diagnosis and treatment monitoring. Collectively, these advances signal a paradigm shift in the management of immune-mediated dilated cardiomyopathy, transitioning from broad immunosuppression to precise, mechanism-based interventions that improve clinical outcomes while minimizing systemic toxicity [49].

Stratified Medicine and Precision Immunotherapy

In recent years, the paradigm of "one-size-fits-all" therapy for dilated cardiomyopathy (DCM) has shifted toward personalized immunomodulation strategies, underpinned by advances in immunophenotyping and single-cell transcriptomics. Stratified medicine seeks to classify patients into subgroups based on immunogenetic, cellular, and molecular profiles that predict disease trajectory and therapeutic responsiveness. This approach holds particular promise for immune-mediated DCM, where clinical heterogeneity is pronounced and response to immunosuppression is variable [45,48].

Immunophenotyping, utilizing multiparameter flow cytometry or CyTOF (cytometry by time of flight), enables the characterization of peripheral and tissue-resident immune cells-such as $CD4^+$ Th1/Th17 cells, $CD8^+$ cytotoxic lymphocytes, regulatory T cells (Tregs), and B-cell subpopulations-along with their activation states and cytokine production profiles [45,47]. Inflammatory signatures marked by elevated Th17 cells and reduced Treg:T-effector ratios, for instance, may predict aggressive myocardial inflammation and guide early initiation of corticosteroids or biologics targeting IL-17 or IL-6 [47,49].

Single-cell RNA sequencing (scRNA-seq) has further advanced our understanding of myocardial immune cell heterogeneity by revealing transcriptional programs associated with immune activation, exhaustion, or tolerance. It can delineate distinct subsets of pathogenic fibroblasts, infiltrating macrophages, and autoreactive lymphocytes in endomyocardial biopsy samples. These insights are critical for identifying patients likely to benefit from specific interventions such as cytokine blockade (e.g., anti-TNF-α or anti-IL-6 therapy), B-cell depletion (e.g., rituximab), or IVIG [48].

Moreover, transcriptional profiling of peripheral blood mononuclear cells (PBMCs) offers a minimally invasive alternative for monitoring immunological shifts during therapy, enabling tapering of corticosteroids or escalation of treatment in non-responders. Combined with serum biomarkers (e.g., IL-6, TNF-α, anti-β_1AR autoantibodies), these techniques support a systems-level approach to decision-making [46].

Ultimately, integrating high-dimensional immune data with clinical phenotyping and genomic information will foster the development of precision immunotherapies tailored to an individual's immune architecture, disease stage, and risk profile. This not only improves outcomes but also minimizes unnecessary immunosuppression and its associated complications [49].

Genetic and Epigenetic Modulators of Immune Response

Advancements in high-throughput sequencing technologies have transformed the understanding of genetic and epigenetic mechanisms underlying immune dysregulation in DCM. A growing body of evidence supports the contribution of both rare and common genetic variants, along with environmentally responsive epigenetic alterations, to the aberrant immune activation observed in DCM [6,7].

Next-generation sequencing (NGS), particularly whole-exome sequencing (WES) and whole-genome sequencing (WGS), has enabled the identification of pathogenic mutations in genes encoding sarcomeric and cytoskeletal proteins (e.g., TTN, LMNA, DES), which predispose individuals to myocardial vulnerability and inflammation [6]. Importantly, variants in immune-regulatory genes-such as TNFRSF1A, IL10, and TLR4-have been implicated in exaggerated cytokine responses and maladaptive innate immunity in viral or autoimmune myocarditis progressing to DCM [7,10].

Beyond the static genome, epigenetic mechanisms serve as critical modulators of immune gene expression in response to environmental triggers such as viral infections or toxins. DNA methylation profiling has uncovered differentially methylated regions in promoter regions of inflammatory cytokines (e.g., IL6, TNFA) and cardiac structural genes, correlating with disease severity and inflammatory burden. These epigenetic marks are particularly enriched in immune effector cells infiltrating the myocardium [14,27].

Histone modifications, such as H3K27 acetylation and H3K9 methylation, also regulate chromatin accessibility at cytokine gene loci and contribute to persistent inflammatory gene expression even after viral clearance. These heritable yet reversible modifications may sustain pathological immune memory in DCM [17,18].

Moreover, microRNAs (miRNAs)-small non-coding RNAs that post-transcriptionally regulate gene expression -have emerged as key regulators of immune pathways in DCM. For instance, miR-155 and miR-21 are upregulated in inflammatory cardiomyopathies and directly modulate the NF-κB signaling cascade and fibrotic gene networks, promoting chronic myocardial inflammation and remodeling [24,42]. Circulating miRNAs are also being investigated as minimally invasive biomarkers of disease activity and immunopathological subtypes.

Together, these multi-omics approaches reveal intricate gene-environment interactions that orchestrate susceptibility and progression in immune-mediated DCM. Integrating genomic and epigenomic profiling with immunophenotyping may yield predictive biomarkers and novel therapeutic targets, ushering in an era of precision cardioimmunology. Continued efforts to build biobanks and patient registries linked to deep phenotyping will be essential to validate these associations and implement them in clinical practice.

4. Conclusions

Dilated cardiomyopathy (DCM) is a complex clinical entity driven by multifactorial etiologies, with immune-mediated mechanisms playing a pivotal role in its pathogenesis and progression. Both innate and adaptive immune systems, while initially protective, can become maladaptive in the setting of persistent activation, genetic predisposition, or viral persistence. Viral myocarditis-especially triggered by enteroviruses-acts as a principal initiator, inducing the release of proinflammatory cytokines, matrix metalloproteinases, and promoting fibrotic remodeling of the myocardium.

The adaptive immune response in DCM is characterized by Th1 and Th17 polarization, with secretion of IFN-γ and IL-17A contributing to myocardial injury and chronic inflammation. B cells are also crucial, producing autoantibodies against β_1-adrenergic receptors, M_2-muscarinic receptors, myosin, troponin, and mitochondrial proteins. These autoantibodies not only serve as diagnostic biomarkers but also exert direct pathophysiological effects, sustaining autoimmune processes even after viral clearance.

Therefore, DCM should be conceptualized not merely as a mechanical failure of cardiac contractility, but as an immune-mediated disorder. Therapeutic strategies such as immunosuppressants, IVIG, immunoadsorption, and interferon -based approaches have shown efficacy in selected patient populations. Continued elucidation of the immunopathogenic pathways in DCM is essential for advancing personalized medicine, wherein the patient's immunological profile guides treatment decisions, risk stratification, and long-term prognosis.

REFERENCES

[1] Mahmaljy H, Yelamanchili VS, Singhal M. Dilated cardiomyopathy. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023 Apr 7.

[2] Schultheiss HP, Fairweather D, Caforio ALP, Escher F, Hershberger RE, Lipshultz SE, et al. Dilated cardiomyopathy. Nat Rev Dis Primers. 2019 May 9; 5(1): 32.

[3] Brownrigg JR, Leo V, Rose J, et al. Epidemiology of cardiomyopathies and incident heart failure in a population -based cohort study. Heart. 2021.

[4] Codd MB, Sugrue DD, Gersh BJ, Melton LJ. Epidemiology of idiopathic dilated and hypertrophic cardiomyopathy. A population-based study in Olmsted County, Minnesota, 1975–1984. Circulation. 1989; 80: 564–72.

[5] Hershberger RE, Hedges DJ, Morales A. Dilated cardiomyopathy: The complexity of a diverse genetic architecture. Nat Rev Cardiol. 2013; 10(9): 531–47.

[6] Wang E, Zhou R, Li T, Hua Y, Zhou K, Li Y, et al. The molecular role of immune cells in dilated cardiomyopathy. Medicina (Kaunas). 2023 Jul 5; 59(7): 1246.

[7] Caforio AL, Keeling PJ, Zachara E, Mestroni L, Camerini F, Mann JM, et al. Evidence from family studies for autoimmunity in dilated cardiomyopathy. Lancet. 1994 Sep 17; 344 (8925): 773–7.

[8] Sozzi FB, Gherbesi E, Faggiano A, Gnan E, Maruccio A, Schiavone M, et al. Viral myocarditis: Classification, diagnosis, and clinical implications. Front Cardiovasc Med. 2022 Jun 20; 9: 908663.

[9] Gebhard JR, Perry CM, Harkins S, Lane T, Mena I, Asensio VC, et al. Coxsackievirus B3-induced myocarditis: Perforin exacerbates disease, but plays no detectable role in virus clearance. Am J Pathol. 1998 Aug; 153(2): 417–28.

[10] Verdonschot J, Hazebroek M, Merken J, Debing Y, Dennert R, Brunner-La Rocca HP, et al. Relevance of cardiac parvovirus B19 in myocarditis and dilated cardiomyopathy: Review of the literature. Eur J Heart Fail. 2016 Dec; 18(12): 1430–41.

[11] Reddy S, Eliassen E, Krueger GR, Das BB. Human herpesvirus 6-induced inflammatory cardiomyopathy in immunocompetent children. Ann Pediatr Cardiol. 2017 Sep-Dec; 10(3): 259–68.

[12] Krych S, Jęczmyk A, Jurkiewicz M, Żurek M, Jekiełek M, Kowalczyk P, et al. Viral myocarditis as a factor leading to the development of heart failure symptoms, including the role of parvovirus B19 infection-Systematic review. Int J Mol Sci. 2024; 25(15): 8127.

[13] Orphanou N, Papatheodorou E, Anastasakis A. Dilated cardiomyopathy in the era of precision medicine: Latest concepts and developments. Heart Fail Rev. 2022 Jul; 27(4): 1173–91.

[14] Gkouziouta G, Karavolias J, Fekos A, Katsianis P, Kourkoveli PH, Cokkinos S, et al. High prevalence of viral genomes and multiple viral infections in the myocardium of adults with "idiopathic" left ventricular dysfunction. Eur Heart J. 2013 Aug; 34 (suppl_1): P3861.

[15] Cusick MF, Libbey JE, Fujinami RS. Molecular mimicry as a mechanism of autoimmune disease. Clin Rev Allergy Immunol. 2012; 42: 102–11.

[16] Sundaresan B, Shirafkan F, Ripperger K, Rattay K. The role of viral infections in the onset of autoimmune diseases. Viruses. 2023 Mar 18; 15(3): 782.

[17] Shim SH, Kim DS, Cho W, Nam JH. Coxsackievirus B3 regulates T-cell infiltration into the heart by lymphocyte function-associated antigen-1 activation via the cAMP/Rap1 axis. J Gen Virol. 2014 Sep; 95(Pt 9): 2010–18.

[18] Kishore J, Kishore D. Clinical impact and pathogenic mechanisms of human parvovirus B19: A multiorgan disease inflictor incognito. Indian J Med Res. 2018 Oct; 148(4): 373–84.

[19] Yanagawa B, Spiller OB, Choy J, Luo H, Cheung P, Zhang HM, et al. Coxsackievirus B3-associated myocardial pathology and viral load reduced by recombinant soluble human decay-accelerating factor in mice. Lab Invest. 2003; 83(1): 75–85.

[20] Jahns R, Boivin V, Hein L, Triebel S, Angermann CE, Ertl G, et al. Direct evidence for a beta 1-adrenergic receptor-directed autoimmune attack as a cause of idiopathic dilated cardiomyopathy. J Clin Invest. 2004 May; 113(10): 1419–29.

[21] Patel PA, Hernandez AF. Targeting anti-beta-1-adrenergic receptor antibodies for dilated cardiomyopathy. Eur J Heart Fail. 2013 Jul; 15(7): 724–9.

[22] Zhang J, Xu H, Li Z, Feng F, Wang S, Li Y. Frequency of autoantibodies and their associated clinical characteristics and outcomes in patients with dilated cardiomyopathy: A systematic review and meta-analysis. Autoimmun Rev. 2025; 24(4): 103755.

[23] Hu C, Wong FS, Wen L. B cell-directed therapy for autoimmune diseases. Clin Exp Immunol. 2009 Aug; 157(2): 181–90.

[24] Nindl V, Maier R, Ratering D, De Giuli R, Z üst R, Thiel V, et al. Cooperation of Th1 and Th17 cells determines transition from autoimmune myocarditis to dilated cardiomyopathy. Eur J Immunol. 2012 Sep; 42(9): 2311–21.

[25] Janeway CA Jr, Travers P, Walport M, Shlomchik MJ. Immunobiology: The immune system in health and disease. 5th ed. New York: Garland Science; 2001.

[26] Liang KP, Kremers HM, Crowson CS, Snyder MR, Therneau TM, Roger VL, et al. Autoantibodies and the risk of cardiovascular events. J Rheumatol. 2009 Nov; 36(11): 2462–9.

[27] Aristizábal B, González Á. Innate immune system. In: Anaya JM, Shoenfeld Y, Rojas-Villarraga A, et al., editors. Autoimmunity: From bench to bedside. Bogotá: El Rosario University Press; 2013.

[28] Goulopoulou S, McCarthy CG, Webb RC. Toll-like receptors in the vascular system: Sensing the dangers within. Pharmacol Rev. 2016 Jan; 68(1): 142–67.

[29] Frantz S, Falcao-Pires I, Balligand JL, Bauersachs J, Brutsaert D, Ciccarelli M, et al. The innate immune system in chronic cardiomyopathy: A European Society of Cardiology (ESC) scientific statement from the Working Group on Myocardial Function of the ESC. Eur J Heart Fail. 2018 Mar; 20(3): 445–59.

[30] Högye M, Mándi Y, Csanády M, Sepp R, Buzás K. Comparison of circulating levels of interleukin-6 and tumor necrosis factor-alpha in hypertrophic cardiomyopathy and in idiopathic dilated cardiomyopathy. Am J Cardiol. 2004 Jul 15; 94(2): 249–51.

[31] Frangogiannis NG. The extracellular matrix in ischemic and nonischemic heart failure. Circ Res. 2019 Jun 21; 125(1): 117–46.

[32] Coffman JA. Enteroviruses activate cellular innate immune responses prior to adaptive immunity and tropism contributes to severe viral pathogenesis. Microorganisms. 2025 Apr 10; 13(4): 870.

[33] Jain P, Jain A, Khan DN, Kumar M. Human parvovirus B19 associated dilated cardiomyopathy. BMJ Case Rep. 2013 Aug 5; 2013:bcr2013010410.

[34] Xu S, Wu Z, Chen H. Construction and evaluation of immune -related diagnostic model in patients with heart failure caused by idiopathic dilated cardiomyopathy. BMC Cardiovasc Disord. 2024; 24: 92.

[35] Perugino CA, Kaneko N, Maehara T, Mattoo H, Kers J, Allard-Chamard H, et al. CD4+ and CD8+ cytotoxic T lymphocytes may induce mesenchymal cell apoptosis in IgG4 -related disease. J Allergy Clin Immunol. 2021 Jan; 147(1): 368–82.

[36] Dandel M. Autoimmunity in cardiomyopathy-induced heart failure and cardiac autoantibody removal by immunoadsorption. J Clin Med. 2025 Feb 1; 14(3): 947.

[37] Bermea K, Bhalodia A, Huff A, Rousseau S, Adamo L. The role of B cells in cardiomyopathy and heart failure. Curr Cardiol Rep. 2022 Aug; 24(8): 935–46.

[38] Yoshikawa T, Baba A, Nagatomo Y. Autoimmune mechanisms underlying dilated cardiomyopathy. Circ J. 2009 Apr; 73(4): 602–7.

[39] Zhang L, Hu D, Li J, Wu Y, Liu X, Yang X. Autoantibodies against the myocardial beta1-adrenergic and M2-muscarinic receptors in patients with congestive heart failure. Chin Med J (Engl). 2002 Aug; 115(8): 1127–31.

[40] Saleh D, Jones RTL, Schroth SL, Thorp EB, Feinstein MJ. Emerging roles for dendritic cells in heart failure. Biomolecules. 2023 Oct 17; 13(10): 1535.

[41] Satoh M, Nakamura M, Saitoh H, Satoh H, Maesawa C, Segawa I, et al. Tumor necrosis factor-alpha-converting enzyme and tumor necrosis factor-alpha in human dilated cardiomyopathy. Circulation. 1999 Jun 29; 99(25): 3260–5.

[42] Li H, Bian Y. Fibroblast-derived interleukin-6 exacerbates adverse cardiac remodeling after myocardial infarction. Korean J Physiol Pharmacol. 2024; 28(3): 285–94.

[43] Pyrillou K, Burzynski LC, Clarke MCH. Alternative pathways of IL-1 activation, and its role in health and disease. Front Immunol. 2020 Dec 18; 11: 613170.

[44] Altara R, Mallat Z, Booz GW, Zouein FA. The CXCL10/ CXCR3 axis and cardiac inflammation: Implications for immunotherapy to treat infectious and noninfectious diseases of the heart. J Immunol Res. 2016; 2016: 4396368.

[45] Nityashree KL, Rachitha P, Hanchinmane S, Raghavendra VB. Advancing precision medicine: Uncovering biomarkers and strategies to mitigate immune-related adverse events in immune checkpoint inhibitors therapy. Toxicol Rep. 2025 Apr 24; 14: 102035.

[46] Pan SY, Tian HM, Zhu Y, Gu WJ, Zou H, Wu XQ, et al. Cardiac damage in autoimmune diseases: Target organ involvement that cannot be ignored. Front Immunol. 2022 Nov 22; 13: 1056400.

[47] Bracamonte-Baran W, Čiháková D. Cardiac autoimmunity: Myocarditis. Adv Exp Med Biol. 2017; 1003: 187–221.

[48] Coutinho AE, Chapman KE. The anti-inflammatory and immunosuppressive effects of glucocorticoids: Recent developments and mechanistic insights. Mol Cell Endocrinol. 2011 Mar 15; 335(1): 2–13.

[49] Naran K, Nundalall T, Chetty S, Barth S. Principles of immunotherapy: Implications for treatment strategies in cancer and infectious diseases. Front Microbiol. 2018 Dec 21; 9: 3158.