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REVIEW

Inflammation and genetics in myo-pericardial diseases: Insights from the Italian Study Group on Cardiomyopathies and Pericardial Diseases

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Abstract

In the past decade, advancements in knowledge on the immune system have partially unveiled the complex interplay between the heart and the immune system. This new branch of cardiology is now called cardio-immunology. It encompasses different areas from preclinical to translational and purely clinical research aiming to identify the relationship between the immune system and different cardiovascular diseases. Inflammatory cardiomyopathies are a heterogeneous subgroup of non-ischaemic cardiomyopathies characterized by left ventricular, or biventricular, dysfunction after an inflammatory insult. Recently, genetic testing allowed to identify specific genotype–phenotype correlation in the diagnosis and, mostly, in the prognosis of different cardiomyopathies. Some pathogenic variants might lead to a clinical phenotype in overlap with inflammatory myocardial diseases and inflammation can be found in cardiac magnetic resonance or endomyocardial biopsies of different cardiomyopathies. Although prognostic predictors of adverse events and indication to immunosuppressive therapies have been identified in myocarditis, data are lacking in the context of genetic cardiomyopathies presenting myocardial inflammation. As for pericardial diseases, genetic variants in immune-related genes, such as *IL1B* have been described, specifically in recurrent pericarditis. A growing body of evidence starting form genetics and cardio-immunology are trying to elucidate the basic mechanisms of the disease and may play a significant role in the understanding the pathophysiology and potentially the treatment of patients. Some examples are represented by arrhythmogenic cardiomyopathy presenting with hot-phases or biopsy-proven myocarditis presenting genetic mutations in specific genes as *TTN* or *DSP*. The aim of this review paper is to highlight the current knowledge and the unmet clinical needs, providing a practical and concise guidance for specific areas of research and management of patients affected by myo-pericardial diseases with overlap between genetics and inflammation, ranging from genetic testing to medical and device therapy.

Keywords acute myocarditis; cardio-immunology; genetic testing; inflammation; inflammatory cardiomyopathies; pericarditis

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Introduction

Cardio-immunology is a discipline studying the interplay between the heart and immune system. This interplay is raising a lot of interest, with studies ranging from basic science to clinical research.

Inflammation is a key player in several cardiovascular pathologies. From promoting cardiac damage in ischaemic heart disease or autoimmune diseases to inflammatory diseases of the myocardium and pericardium, the pathogenesis is often complex and determined by the interplay among genetic background, inflammation and autoimmunity.

The connection between the immune system and cardiovascular pathologies has been first described in coronary heart disease and is nowadays a trending topic in heart failure (HF), but its role as a potential therapeutic target in myo-pericardial diseases is currently under investigation.

This review aims to analyse current evidence on this interplay between inflammation, immune system and individual genetic background in myocardial and pericardial diseases in order to propose a precision approach for these conditions, not so rare in clinical practice.

Physiopathological mechanisms of inflammation in cardiovascular diseases

Inflammatory response arises after tissue or organ exposure to an endogenous or exogenous harmful stimulus, aiming to resolve the tissue damage and to initiate the healing process.

Activation of the innate immunity is the basic response to infectious or non-infectious insults. It relies on the activity of neutrophils (which can migrate in tissues and amplify the inflammatory response), as well as monocytes, macrophages, dendritic cells and mast cells.[1] Innate immunity is activated by pattern recognition receptors (PRRs) expressed on most human cells. These receptors can be divided in toll-like receptor (TLR), nod-like receptors (NLR), pentraxin (such as CRP and amyloid P), RIG-I like receptors and C-type lectin receptors and bind PAMPs (produced by pathogens like bacteria) and DAMPs (peptides released by necrotic or injured cells) to activate the inflammatory cascade.[2,3] Proinflammatory cytokines [such as TNF, interleukin (IL)-1B, IL-6 and IL 8] and chemokines are important mediators of these processes. Cytokines and chemokines can bind specific receptors on target cells, activating leukocytes subpopulations: in particular, monocytes and macrophage are the main immune cells in human and experimental myocarditis[4] and CC motif chemokines, such as CCL2, CCL3, CCR2 and CCL5 are elevated in HF. [5] Monocytes can differentiate in pro-inflammatory macrophages, secreting TNF and IL-6, or anti-inflammatory ones, contributing to tissue repair. Dendritic cells [or antigen-presenting cells (APC)] ingest the antigens and migrate to the lymph nodes and the spleen to present them to naïve T and B cells. Innate immunity activity is usually operating within few days or weeks from the initial noxa and may trigger a subsequent autoimmune response.

The adaptive immune response relies on T and B cells: T cells are lymphocytes that express CD3 and T-cell receptor, an antigen receptor, and can be divided in CD8+ (cytotoxic lymphocytes) and CD4+, while B cells can bind antigens with B-cell receptor and can differentiate in plasma cells, producing antibodies, or in immune memory B cells.

T cells originate in the bone marrow and maturate in the thymus, where CD4+ cells can differentiate in T helper cells and T regulatory cells (Treg), which inhibit the immune response.[6]

Specifically, T helper cells can be divided in Type 1 T helpers (Th1), Type 2 helpers (Th2) and T helper 17 (Th17): Th1 activate macrophages through IL-2, TNFβ and IFNγ production and regulate cell-mediated immunity, Th2 have a role in modulating B cells, antibody production, eosinophil activation and macrophage inhibition through IL-4, IL-5, IL-10 and IL-13, Th17, through production of IL-17 an IL-22, are responsible of mucosal immunity and have been closely associated to autoimmunity in humans.[7]

T cells are considered the main effectors of cardiac damage both on autoimmune and viral myocarditis, especially CD4+: in experimental viral myocarditis, CD4+ deletion was associated to myocarditis resolution, whereas CD8+ deletion alone did not lead any change.[8] Interestingly, Th17 levels are significantly elevated in human myocarditis presenting with HF.[9]

Treg, on the other hand, have a protective role from myocarditis: their reduction leads to increased Th17 response and more severe forms of autoimmune myocarditis in mice.[10]

Immune cross-talks in heart failure

Few data are available on the role of inflammation and the immune system in HF and myo-pericardial diseases, although systemic inflammation has been recognized in the pathophysiology and progression of both acute and chronic HF. The relationship between inflammation and HF is bidirectional and is consistent across the whole spectrum of ventricular function. In HF with reduced ejection fraction (HFrEF), a chronic inflammatory status, caused by persistent myocardial injury and continuous activation of proinflammatory pathways, has been described,[11] but a stronger association has been found in HF with preserved ejection fraction (HFpEF), where elevation of inflammatory biomarkers (i.e., hsCRP)

and a systemic inflammatory state due to comorbidities (such as hypertension, diabetes, chronic kidney disease and obesity) are increasingly targeted in ongoing clinical trials.[11–14]

The pro-inflammatory state found in HF stimulates both expression of adhesion molecules and reactive oxygen species (ROS) production by microvascular endothelial cells. On one side adhesion molecules, such as vascular cell adhesion molecule and E-selectin, recruit inflammatory cells, on the other side ROS reduce nitric oxide (NO) levels and protein kinase G (PKG) function in myocardial cells, leading to titin (*TTN*) hyperphosphorylation, hypertrophy and stiffening of cardiomyocytes and, eventually, collagen deposition in the myocardium.[15,16]

The innate immunity activation by TLRs, expressed on cardiomyocytes, through the binding of DAMPs and PAMPs stimulates the nuclear translocation of NF-κB and the formation of the NLRP3 inflammasome, a cytosolic multiprotein complex that induces the release and activation via caspase-1 of IL-1β and IL-18: these activated cytokines promote the expression of IL-6 and TNFα, expanding once more the inflammatory response.[17] The so-called 'IL-1 cascade' induces systolic dysfunction by inhibiting L-type calcium channels and desensitizing beta-receptors alongside impairing cardiomyocyte relaxation and diastolic dysfunction through the inhibition of the sarcoplasmic reticulum.[18] Eventually, this cascade leads to the recruitment of monocytes from the bone marrow and spleen that infiltrate the heart (the so-called 'cardio-splenic axis' of HF).[9]

TNFα, associated with both impaired diastolic and systolic function and produced by macrophages and cardiomyocytes, has a negative inotropic effect and promotes HFrEF development through the uncoupling of beta-adrenergic receptor and disruption of calcium homeostasis as well as the induction of cardiomyocyte hypertrophy, fibrosis and apoptosis.[19,20] On the other hand, intense TNFα blockade with high dose of infliximab and etanercept led to increased HF hospitalization rates, suggesting a cardioprotective role of TNFα signalling.[21,22]

IL-6, a pro-inflammatory cytokine produced by immune cells, cardiomyocytes and fibroblasts, stimulates liver CRP production, contributes to the development of chronic HF and likely promotes diuretic resistance.[23,24] High IL-6 levels correlate with mortality both in acute and chronic HF and have been associated with severe presentation and poor outcomes in acute myocarditis[25] (*Figure* 1).

Galectin 3, a DAMP, is elevated in patients with symptomatic HF and is recognized as a prognostic marker in HFrEF, as well as sST2 (soluble suppression of tumorigenicity 2), which seems to improve risk stratification regardless of left ventricular (LV) function and N-terminal pro–B-type natriuretic peptide levels.[26,27]

The crosstalk between RAAS system and immunity in HF is extremely tight. Angiotensin II, overexpressed in HF, is a chemokine for immune cells in the presence of cardiac stress, at the same time angiotensin-converting enzyme (ACE) participates both in the differentiation of monocytes in macrophages and in antigen presentation through MHC I and MHC II receptors and aldosterone increases the production of pro-inflammatory cytokines by macrophages, stimulating tissue fibrosis.[28]

Regarding humoral immunity, cardiac autoantibodies against beta receptors, troponin I, myosin, N/K ATPase and mitochondrial proteins are frequently found in patients with HF and are related to arrhythmias and sudden cardiac death.[29] Furthermore, prospective studies observed the association of cardiac autoantibodies with asymptomatic LV dilatation in relatives of dilated cardiomyopathy (DCM) patients.[30]

Genetic background and inflammation mechanisms in cardiomyopathies

Knowledge on the interaction of inflammation and genetic background in cardiomyopathies is limited, but research on this field is currently expanding.

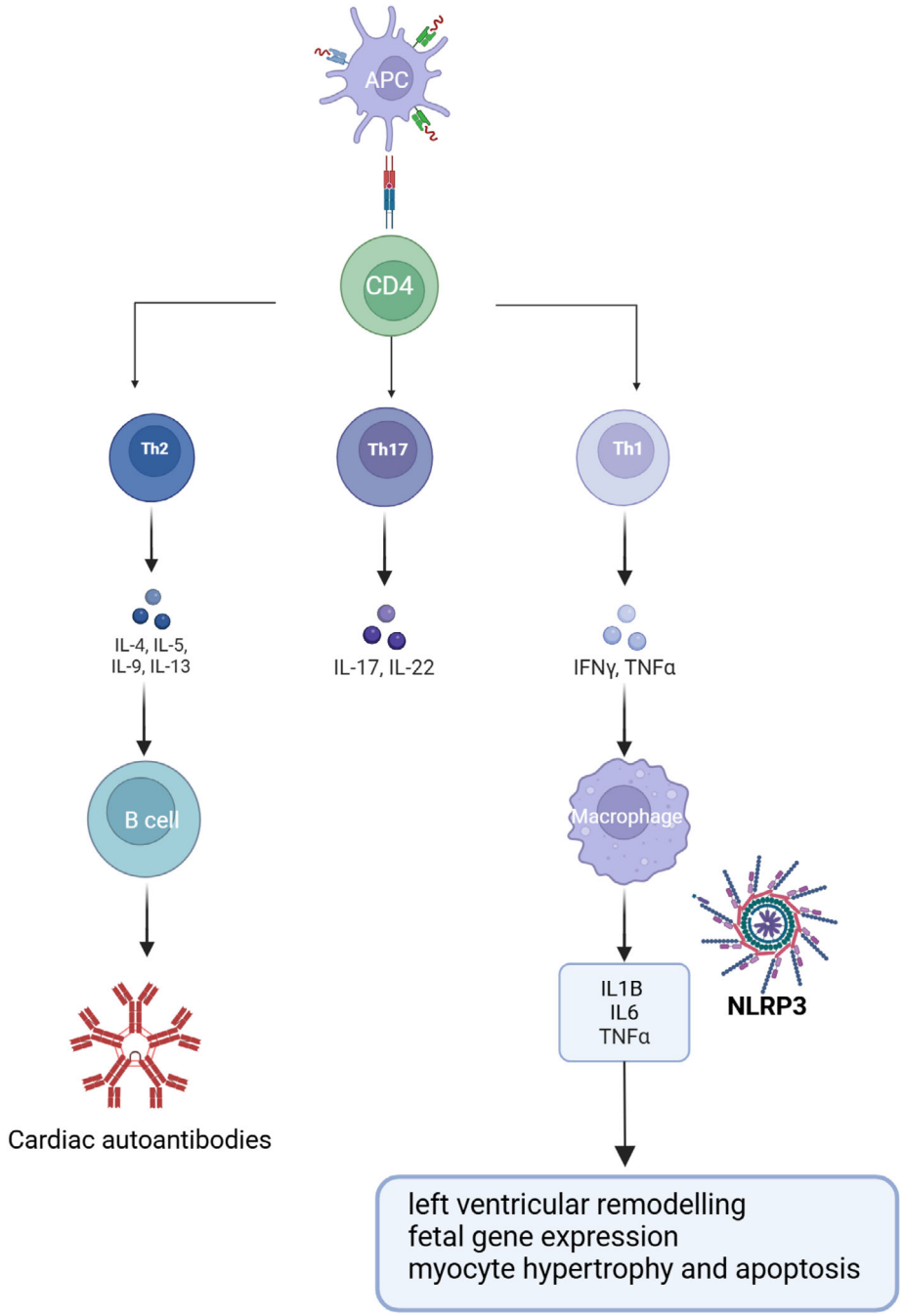
In monogenic and polygenic DCM, arrhythmogenic cardiomyopathy (ACM) and hypertrophic cardiomyopathy (HCM), evidence of sterile inflammation has been described on endomyocardial biopsies. At the same time some patients presenting with clinical acute myocarditis were found to be carriers of variants in cardiomyopathy-related genes: these findings reinforce the concept of a link between inflammation and genetics. Although prognostic predictors of adverse events in myocarditis have been identified, data are lacking in the context of genetic cardiomyopathies presenting myocardial inflammation, and the role of immunosuppression is still under discussion.[31]

DCM

Endomyocardial biopsy (EMB)-proven myocarditis can progress in up to 30% of cases to inflammatory DCM, defined as myocarditis in association with ventricular dysfunction and remodelling[32]: this correlates with poor in-hospital and long-term prognosis.[33,34]

Evolution from myocarditis to DCM seems to be associated with persistent chronic inflammation at EMB and, in cases of viral aetiologies, virus persistence in the myocardium, but a genetically determined predisposition to cardiac dysfunction following viral infections has been previously described in the 'second hit theory'.[35] In fact, viruses or other microbial agents are more likely to induce myocardial inflammation when mutations in sarcomeric or cytoskeletal proteins (i.e., Titin, Troponin I and Desmin) are present, predisposing to systolic dysfunction and arrhythmias.[36] In addition, impaired

Figure 1 Innate and adaptive immune mechanisms in heart failure: activated by DAMPs and PAMPS, APC cells present the antigens to naïve T cells, which can differentiate in Th1, Th2 and Th17. Th1, through TNFα and IFNγ, expands the inflammatory response and activates pro-inflammatory macrophages and the release of IL-1β, TNFα and IL-6. These cytokines, through pleiotropic mechanisms, induce cardiomyocytes dysfunction and apoptosis, correlating with heart failure development and poor outcomes. Th2, releasing IL-4, IL-5 and IL-9, modulates B cells activity and antibodies production: cardiac autoantibodies are frequently found in heart failure patients and correlate with worse prognosis (see main text). IL, interleukin.



TTN phosphorylation was observed in animal models of coxsackievirus B3 myocarditis, leading to increased levels of IL-6 and LV dysfunction, whereas IL-6 receptor blockade improves *TTN* function and then LV ejection fraction (LVEF).[37,38] In knockout mouse models, multiple other genes involved in cardiomyopathies have been linked to increased inflammatory signalling, such as *DMD*, *PLN* and *BAG3*.[39,40] Moreover, *LMNA* variants increase the expression of Hsp70, a pro-inflammatory protein, and the degree of inflammation seems to correlate with disease severity.[41]

Interestingly, DMD-mutated animal models show macrophages and T cells infiltrates in the heart, and myocardial susceptibility to viral infection has been reported in patients with DCM and DMD mutation, correlating to poor outcome.[40,42]

ACM

The immune response in ACM is represented mostly by a lymphocytic and macrophagic myocardial infiltration and an activation of the innate immunity in cardiomyocytes, related to the proinflammatory activity by GSK3B, through NF-κB cascade. Experimental models on small animals and induced pluripotent stem cell-derived cardiomyocytes showed that genetic mutations in *PKP2*-induced NF-κB activation and immune mediators' expression in the heart. NF-κB production by ACM cardiomyocytes seems to contribute to disease development.[43]

Myocarditis-like features are increasingly recognized also in ACM: histological myocarditis is frequently found in ACM patients experiencing sudden cardiac death (SCD).[44] Moreover, cardiac magnetic resonance (CMR) tissue characterization shares some aspects with acute myocarditis such as evidence of oedema and late gadolinium enhancement (LGE). Interestingly, variants in desmoplakin (DSP), a desmosomal protein whose variants are strongly linked to ACM, have been found to be associated to episodes of chest pain and troponin release, similar to the pseudo-infarct presentation of acute myocarditis, in the so-called 'hot-phases' of the disease.[45] These hot-phases affect predominantly young male adults and seem to have a role in the progression of the disease.[46,47] Differential diagnosis between acute myocarditis and hot-phase cardiomyopathy represents an unmet challenge for the clinician: some red flags, such as positive family history of cardiomyopathy, recurrent episodes of myocarditis, persistent troponin release, a LGE ring-like pattern on CMR, an EKG suggestive of cardiomyopathy (i.e., low voltages, T wave inversion) and persistent severe LV dysfunction on optimized medical therapy, should raise the suspicion of a cardiomyopathic background.[48,49] In these patients, a comprehensive characterization through imaging techniques [CMR, fluorodeoxyglucose (FDG)-positron emission tomography (FDG-PET)], endomyocardial biopsy and genetic testing for cardiomyopathy should be preferred. Considering evidence of heterogeneity in EMB interpretation, patients with a clinically suspected hot-phase needing EMB have to be referred to high-volume centres with experienced cardiovascular pathologist in order to obtain a correct diagnosis through standardized methods.[50]

Interestingly, FDG-PET allows the detection of myocardial inflammation when CMR is not feasible (i.e., arrhythmias, presence of non-CMR-compatible implanted devices), and a study is ongoing comparing the two imaging techniques in suspected myocarditis.[51,52]

Furthermore, persistence of (LV dysfunction may be linked to *TTN*-truncating variants (*TTN*tv) in patients affected by lymphocytic myocarditis[53] and EKG abnormalities consistent with ACM (negative waves in V1-V3, in V5-V6 and in inferior leads) have been reported in hot-phase patients.[48] Despite the usefulness of those tools, their routine use in clinical practice requires future evidence.

Our suggested clinical management in the differential diagnosis between acute myocarditis and hot-phases is shown in *Figure* 2.

HCM

In HCM, differently from DCM and ACM, no evidence of myocarditis (as defined by EMB criteria) has been described in post-mortem heart examinations of patients who died suddenly.[54] While some studies have described the presence of oedema in T2-weighted sequences on CMR, their correlation with adverse outcomes, such as life-threatening arrhythmias, disease progression and elevation of cardiac biomarkers of acute myocardial injury, remains currently debated.[55] Nevertheless, sterile myocardial inflammation has been found in autopsies of patients affected by hypokinetic end-stage HCM, possibly representing a reactive response to severe myocardial injury.[54]

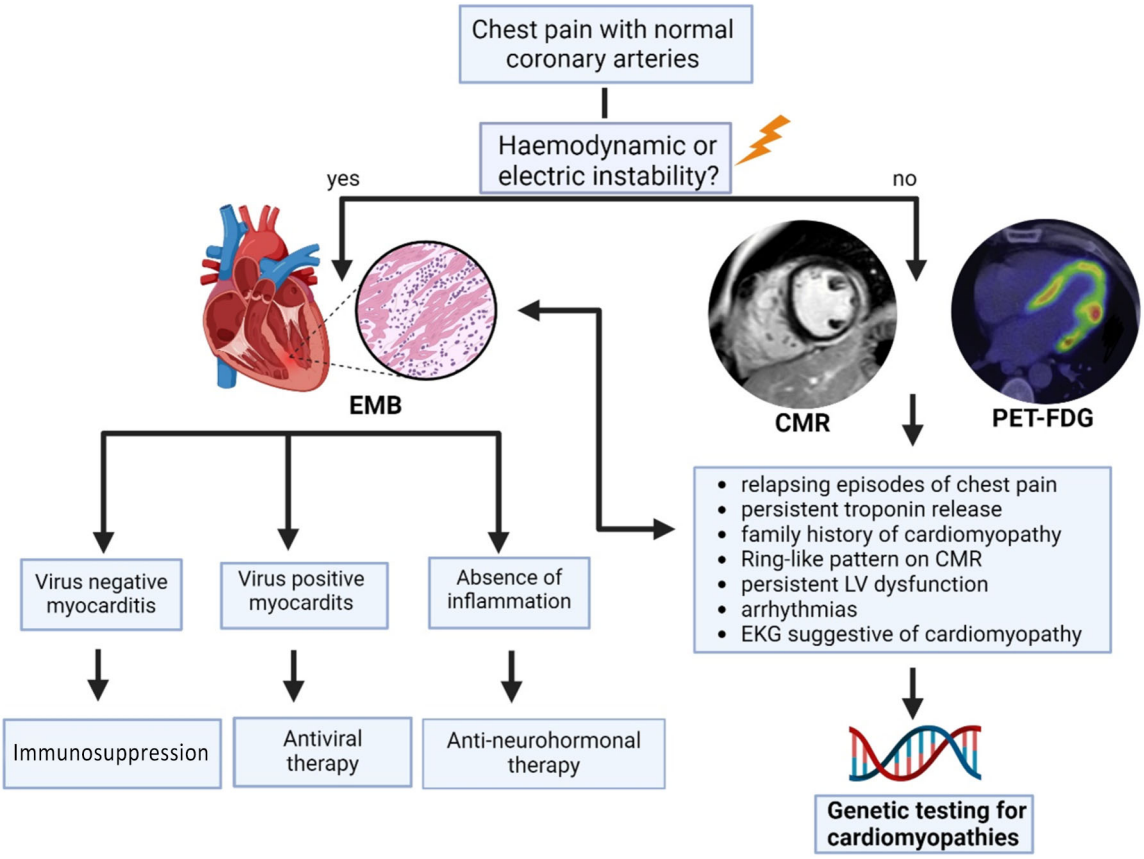
Fabry disease

There is accumulating evidence, both in cardiac tissue samples and imaging findings (CMR), of a role of inflammation in the pathogenesis and progression of cardiac disease in Fabry disease.[56] Substrate deposition of sphingolipids (as Gb3 and lyso-Gb3) can directly trigger a chronic inflammatory state and activate immune system as antigens when presented to natural killer T cells. The role of inflammation as a potential target of future therapies is under investigation.[57]

Autoimmunity

Another challenging topic is the overlap between genetically determined cardiomyopathies and autoimmunity. Chronic inflammatory cardiomyopathy can develop in the background of systemic autoimmune diseases.[58] At the same time, a role of autoimmunity as a shared mechanism in ACM, inflammatory DCM and myocarditis has been suggested because autoantibodies targeting intercalated disc component (AIDA), anti-DSG-2, anti-*TTN* and anti-myosin heavy chain have been found in affected patients. In studies on arrhythmogenic right ventricular cardiomyopathy and ACM, the presence of AIDA and AHA and anti-DGS2 levels were associated with disease activity and severity in terms of lower LVEF, non-sustained ventricular tachycardia and need for ICD implantation.[59] Mutant proteins might be recognized as autoantigens, directing the immune response against cardiomyocytes.

Figure 2 Suggested clinical management in the differential diagnosis between acute myocarditis and 'hot-phases'. The presence of 'red flags', such as relapsing and invalidating episodes of chest pain, chronic release of troponin, family history for cardiomyopathy/SCD, ring like late gadolinium enhancement (LGE) on CMR, persistent left ventricular dysfunction, electrocardiogram compatible with cardiomyopathy, should alert the clinician to perform a comprehensive and multiparametric characterization, including genetic testing and endomyocardial biopsy, even in the absence of haemodynamically and/or electrical instability. CMR, cardiac magnetic resonance; LV, left ventricular.



In addition, a role of molecular mimicry between cardiac proteins and commensal gut microbiome in autoimmune myocarditis has been observed in animal models, and an interplay between genetic predisposition, bacterial antigens and inflammation has been proposed in the progression of acute myocarditis to chronic inflammatory cardiomyopathy.[60] If these findings will be confirmed in clinical trials, targeting the microbiome through dietary interventions, probiotics and antibiotics in genetically predisposed patients might increase the likelihood of recovery and improve patient outcome.[61]

Genetics, inflammation and autoimmunity in myocarditis and pericarditis

Myocarditis is classified as a non-genetic disease with possible aetiologies ranging from viral infection to toxicity and autoimmunity.[62] Acute myocarditis can progress to chronic inflammatory cardiomyopathy, presenting with ventricular dysfunction and/or remodelling.

Familial cases of myocarditis have been described having a hereditary component and, especially when affecting children and characterized by lymphocytic infiltrate at EMB, linked to genetic mutations.[63] Both sarcomeric and desmosomal variants have been identified in patients with acute myocarditis,[64] and a high prevalence of *TTNtv* was observed in patients with EMB-confirmed lymphocytic myocarditis.[53]

In a recent meta-analysis on the prevalence of P/LP variants in acute myocarditis, DSP variants were described to be more prevalent in patients with uncomplicated myocarditis, whereas sarcomeric variants, especially *TTNtv*, were found in patients presenting complicated forms (i.e., acute HF at onset, reduced LVEF and ventricular arrhythmias). Also, younger age at onset correlated with more severe clinical presentation and higher prevalence of P/LP variants in sarcomeric genes.[65]

Finally, pathogenic variants in cardiomyopathy related genes, such as *FLNC*, *BAG3* and *RBM20*, have been observed in patients with acute myocarditis presenting with cardiogenic shock and electrical instability.[66]

Interestingly, genetic variants in immune-related genes are associated with experimental autoimmune myocarditis in murine models; in particular, MHC II-deficient mice can develop acute myocarditis and show increased susceptibility to immune checkpoint inhibitor-induced myocarditis and acute HF. Further studies are needed to shed light on the role of these genetic defects in humans.

As for other histotypes of myocarditis, in cardiac sarcoidosis, a classic Mendelian inheritance was described in Blau syndrome, an early and aggressive form linked to CARD15 mutations causing constitutive NF-κB activation,[67] but in giant cell myocarditis, although expression of genes involved in Th1 activation is upregulated,[68] disease genes have not been identified yet.[69]

Genetic factors are increasingly considered in the pathogenesis of recurrent pericarditis. About 10% of patients with recurrences may have a family history of pericarditis suggesting a genetic predisposition[70] that has been confirmed in selected cases with idiopathic recurrent pericarditis for genes involved in autoinflammatory diseases, such as the *TNFRSF1A* gene,[71] *MEFV* variants[72] and variants at the IL-1 gene locus.[73] Current evidence is limited to the analysis of specific genes, mainly involved in autoinflammatory diseases, a group of genetic disorders characterized by primary dysfunction of the innate immune system and caused by mutations of genes involved in the regulation of the inflammatory response. Genetic predisposition may be important in patients with a family history of pericarditis, multiple recurrences and a prolonged disease course despite anti-inflammatory therapies. It can improve the knowledge of the disease and how to individualize treatments, reducing therapy failures and occurrence of new recurrences.[74]

Allergy, anaphylaxis and cardiac damage

Allergens can induce systemic and tissue immune-mediated reactions up to severe anaphylaxis. The implicated molecules are released from inflammatory cells and include IL-1α, IL-1β, IL-6, IL-10, IL-17A, IL-12 p70, IL-18, IFNα, TNF and an additional inflammatory cluster defined by thrombopoietin, IL-33, IL-16, IL-21, IL-23, IFNλ, eotaxin and eotaxin-3, which were demonstrated to cause even severe disease.[75] Multiple effectors, such as IL-5, IL-13, IgE, eosinophils, and type 2 antibody isotype IgE, were also found in severe COVID-19 disease, with increase continued during the course of the disease.[76] The allergic myocardial ischaemia is a long-standing syndrome, ranging from angina to myocardial infarction. It represents the manifestation of severe endothelial dysfunction belonging to the group of myocardial infarction with nonobstructive coronary arteries syndromes. Allergic angina was early described 30 years ago and then identified by American researchers as the Kounis syndrome.[75]

The pathophysiology of Kounis syndrome encompasses several inflammatory mediators, released during mast cell activation and degranulation, according to four types of reactions: (1) mast cell activation by allergens cross-linking allergen-specific IgE bound to high-affinity platelet Fc epsilon receptor 1 (FcεR1); (2) activation by non-IgE-mediated degranulation via the complement C1q, C3a C4, C5a and Factor B (anaphylatoxins).[75] This complement pathway activation involves IL-5 and tryptase and is much more common than recognized, in patients who developed renal failure or fatal cerebral events during COVID-19 infection; (3) activation by low-affinity mast-related G protein-coupled receptor X2 (MRGPRX2) that may activate mast cells via non-Fcε receptors; ny neuropeptides, including corticotropin-releasing hormone, neurotensin (NT) and substance P (SP) via high-affinity receptors.[77]

Targeting inflammation and targeting genes

Targeting inflammation in myocarditis and pericarditis

Patients with acute myocarditis or inflammatory cardiomyopathies with significant LV dysfunction (i.e., LVEF $<$ 50%) are treated with anti-neurohormonal therapy [i.e., ACE inhibitors, angiotensin receptor blocker (ARB), beta-blockers, angiotensin receptor/neprilysin inhibitor, sodium-glucose cotransporter-2 inhibitor (SGLT2i) and mineralocorticoid receptor antagonists (MRAs)] for at least 6 months.[78] Interestingly, some of these treatments have demonstrated some immunomodulatory properties in HF. Beta-blockers reduce cytokines levels, and CCL2-mediated ACE inhibitors decrease CCL2, IL-6 and CRP and downregulate T-cell proliferation; ARBs promote T-cell differentiation towards Th2 and Treg and MRAs, such as eplerenone, stimulate the shift of monocytes towards a healing phenotype.[28,79] Furthermore, SGLT2is have been shown to suppress the NLRP3 inflammasome and cytokine production.[80]

Immunosuppression is recommended by current guidelines in EMB-proven myocarditis refractory to optimized medical therapy (OMT) and fulminant myocarditis (after ruling out a viral aetiology), other than in specific cases such as giant cell, eosinophilic myocarditis and sarcoid myocarditis.[78] Ongoing trials could give important answers on this topic, mostly in the setting of fulminant myocarditis.[81]

Focusing on chronic inflammatory cardiomyopathies, TIMIC trial first showed an improvement in cardiac function of 10% in patients with EMB-proven virus negative chronic inflammatory cardiomyopathy when treated with prednisone and azathioprine compared with controls,[82] and a randomized clinical trial meta-analysis showed similar results.[83] An observational study reporting the long-term follow-up of

TIMIC trial patients confirmed a persistent improvement of cardiac function and dimensions, but also a risk reduction of cardiovascular death and heart transplant in the treated group, compared with a propensity-matched control cohort.[84] Yet scarce data are available on treatment timing, duration and safety: clinical trials are currently focusing on these questions [IMPROVE-MC (NCT04654988—1 year azathioprine and 6 months prednisone vs. placebo), TRINITY (NCT05570409—mycophenolate + prednisone for 6 months)].

Interestingly, a recent propensity-matched study observed the efficacy of tailored immunosuppression in EMB-proven myocarditis, based on histotype, clinical presentation and patient characteristics: prolonged immunosuppression managed by a multidisciplinary cardio-immunology team was effective and safe across the whole myocarditis clinical spectrum. These findings raise the importance of an individualized and multidisciplinary approach in the treatment of myocarditis, like other immunological diseases.

In any case, large multicentre trials with adequate statistical power to detect differences in survival are needed to prove the role of immunosuppression in inflammatory cardiomyopathies.

As described above, the NLRP3 inflammasome is crucial in the pathogenesis of myocarditis/pericarditis through IL-1 production. However, while IL-1B inhibition through monoclonal antibodies has been demonstrated beneficial in patients with ischaemic HF,[14] recurrent pericarditis[85] and AHF,[86,87] a recent trial exploring the effect of anakinra in myopericarditis showed neutral results.[88] On the contrary, based on its safety and efficacy in the treatment of polyserositis in familial Mediterranean fever, colchicine has been proven efficacious to treat and prevent recurrences of pericarditis and myopericarditis.[89]

Currently, anti-IL-1 agents are targets for the treatment of corticosteroid-dependent and colchicine-resistant forms of recurrent pericarditis with an inflammatory phenotype (fever and/or elevation of C-reactive protein at presentation).[90]

Targeting inflammation and targeting genes in cardiomyopathies

Data are lacking regarding the therapeutical approach to genetically determine cardiomyopathies presenting myocardial inflammation, and multicentric clinical studies are needed to assess the efficacy of immunomodulatory and immunosuppressive therapies in this setting and to identify new targets. Interestingly, a recent case series reported significant reverse remodelling with anti-neurohormonal therapy in patients with hot-phases presenting apoptosis, rather than inflammation, on EMB.[49]

In a large retrospective cohort of suspected non-dilated LV cardiomyopathy with arrhythmic phenotype, evidence of

Table 1 Future perspectives of immunomodulation in myo-pericardial diseases.

	Therapy	Pathology	Study	Outcome
Cytokines				
IL-1B receptor antagonists	Anakinra vs placebo	Acute myocarditis	ARAMIS[95]	No difference in days free from myocarditis complications in the two groups
	Recently decompensated HFrEF and systemic inflammation	REDHART2 (Phase II RCT)[87]	pVO_2 at 24 weeks (ongoing)	
IL-6 monoclonal antibodies	Ziltivekimab (IL-6 antibody)	HFmrEF, HFpEF with systemic inflammation	HERMES (RCT)[13]	CV death, heart failure hospitalization/urgent HF visit (on going)
IL-10	Recombinant human IL-10 (hr-IL10)	Acute viral myocarditis	Animal models (mouse)[96]	No human studies to date
B cells				
CD20	Rituximab	Inflammatory DCM refractory to steroids with CD20 persistence on EMB	Case series[97]	LVEF, EDV, NYHA class and NT-proBNP improvement
Circulating antibodies	Non-specific immunoadsorption	Inflammatory cardiomyopathy	Multicentric Study of Immunoadsorption in DCM (NCT00558584)	LVEF improvement (ongoing)
T cells				
Treg	HMSc	Non-ischaemic DCM	POSEIDON-DCM trial,[98]	Treg increase, TNFα levels reduction LVEF improvement, lower MACE
Treg administration	CVB3-induced myocarditis	Animal models (mouse)		

Abbreviations: CV, cardiovascular; DCM, dilated cardiomyopathy; EDV, end-diastolic volume; HF, heart failure; HFmrEF, HF with mid-range ejection fraction; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; IL, interleukin; LVEF, left ventricular ejection fraction; MACE, major cardiovascular event; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RCT, randomized clinical trial.

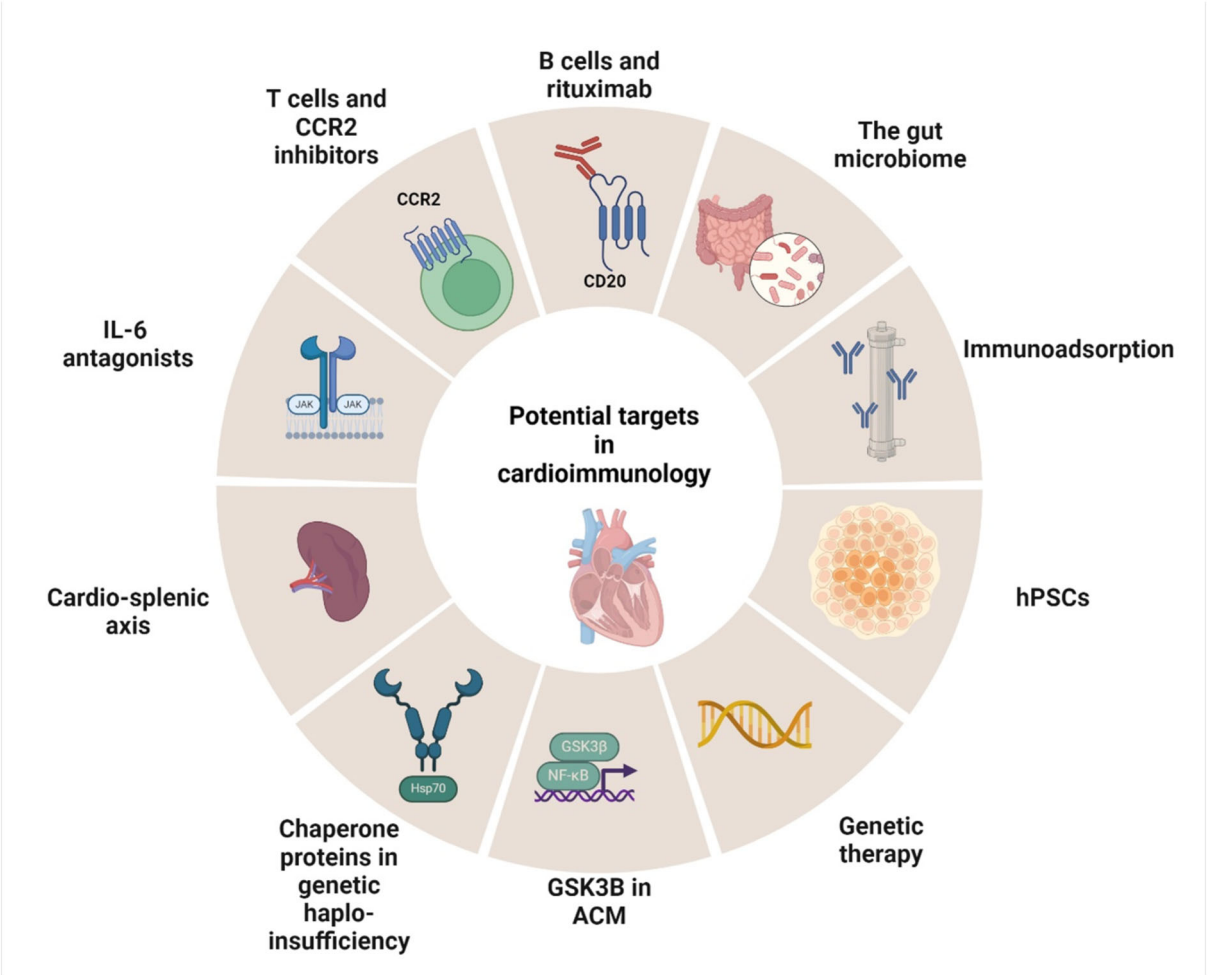
active myocardial inflammation on EMB was an independent predictor of cardiac death, heart transplantation or malignant VA, and immunosuppressive treatment was associated with a lower risk of MACE.[91]

As for the impact of genotyping inflammatory cardiomyopathies, a multicentric study assessing the prevalence of genetic variants in patients with acute myocarditis found that some variants are associated with a specific phenotype (i.e., *TTN* with reduced LVEF and *DSP* with preserved LVEF) but also that having a genetic mutation was a negative prognostic factor.[64] Moreover, immunosuppressive treatment in inherited cardiomyopathy with evidence of myocardial inflammation showed to prevent arrhythmia recurrence and SCD, following preliminary data.[92]

As novel pharmacological approaches are being developed to target specific cardiomyopathies through gene replacement or small molecules, targeting chaperone proteins in genetic cardiomyopathies caused by haploinsufficiency (e.g., *TTNtv* and truncating desmosomal variants) is another potential therapeutic approach.[93] Beyond the genetic approach, innovative immune-modulation therapies are under study in cardiomyopathies with genetic background: NF-κB inhibition with a small molecule (Bay 11-7082) proved to prevent disease onset in ACM animal models.[94]

On top of limited availability of genetic testing, lack of standardized genetic panels and high prevalence of variants of uncertain significance, phenotypic variability of cardiomyopathies, caused by both genetic background and environ-

Figure 3 Future perspectives in cardio-immunology. Multiple therapeutical targets are currently understudy: IL-6 receptor inhibition is showing results in animal models,[91] as well as monocyte inhibition via CCR2 in experimental models of acute myocarditis.[92,93] Rituximab was effective in inflammatory cardiomyopathies with high CD20 levels on EMB[89] and a randomized clinical trial has been recently completed on the use of immunoadsorption in inflammatory dilated cardiomyopathy. The cardio-splenic axis could be targeted by IL-1B inhibitors or Treg cells transfer, blocking the recruiting of pro-inflammatory monocytes.[99,100] A potential therapeutic approach to genetically determined cardiomyopathies caused by haploinsufficiency (i.e., titin-truncating variants, truncating desmosomal variants) might be modulating chaperone proteins such as Hsp70, responsible of sarcomere homeostasis, to reduce the rate of protein degradation.[85] IL, interleukin.



mental factors, represents a challenge in identifying the therapeutic targets and the timing for treatment intervention. Clinical trials on the early disease phases, where inflammation and active immune activation might be present, are needed to confirm evidence from animal models and small trials on humans (see *Table* 1 and *Figure* 3).

Finally, because a multimodal approach, including imaging techniques (CMR and FDG-PET), histology (EMB) and genetic testing, is nowadays essential to respond to patients' needs, the use of complex models, algorithms and artificial intelligence may represent a new frontier for future research (graphical abstract).

Conclusions

The complex interplay between genetics, the inflammation and immune system in myocardial and pericardial heart diseases is rapidly emerging, with a particular focus on genetic variants underlying these conditions in specific patients. In this perspective, new therapeutic targets and new biomarkers for following myocardial and pericardial diseases could be available in the next future, based on cardio-immunology developments. However, further studies on the role of myocardial inflammation in genetically determined cardiomyopathies are needed, considering that no clear causal role has yet been identified. Larger trials selecting patients based on immunophenotyping and genotype will allow us to identify optimal targets and hopefully develop new therapies for myocardial and pericardial diseases.

Conflict of interest statement

None declared.

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