What Is the Role of the Inflammation in the Pathogenesis of Heart Failure?

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Abstract

Purpose of Review In heart failure, whether it is associated with reduced or preserved ejection fraction, the immune system is activated and contributes to heart remodeling and impaired function.

Recent Findings Studies indicate that cells of the immune system not only play a role in the pathology but are also critical regulators of heart function. Knowledge about the role of the immune system driving heart failure will lead to the development of new targets to this system, particularly in those patients that, despite the apparent wellness, relapse and worsen.

Summary In this review, we will address the diverse mechanisms that trigger inflammation and their impact on heart failure progression.

Keywords Heart failure • Acute inflammation • Systemic inflammation • Inflammasome • Reduced ejection fraction and preserved ejection fraction

Introduction

Inflammation is a well-orchestrated process in which immune cells and tissues work together against pathogens and in the resolution of locally injured tissues to heal and restore homeostasis [1]. When acute local inflammation becomes chronic, it evolves systemic and becomes detrimental to our health [2]. Systemic chronic inflammation is a condition in which lifestyle plays an important role and can lead to non-communicable diseases such as cardiovascular disease (CVD) [3]. For instance, chronic stress and western diet are well-known factors that contribute to persistent sterile inflammation (induced by self-antigens) and the appearance of said diseases [3–5]. Inflammatory byproducts such as C-reactive protein (CRP), cytokines, and antibodies are associated with severity and with an increased risk of mortality [6–8]. Moreover, systemic inflammation predicts all-cause mortality [9, 10]. Recently, Alpert, Shen-Orr, and colleagues generated an immunological age metric through cellular immune profiles and cytokine responses, which describe immune function better than their chronological age. In addition, it predicts all-cause mortality, including CVD [11]. In agreement, Furman, Faustin, and colleagues showed that elderly subjects with increased IL-1β and oxidative stress levels were associated with inflammasome genes that correlate with mortality and CVD risk [12].
Also, the neurohormonal pathways: renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system (SNS), and natriuretic peptides system, trigger immune pathway activation [13, 14]. Thus, the fact that these mechanisms promote inflammation and that inflammation leads to HF indicates that the immune system plays a central role in HF progression. Moreover, recent studies indicate that cells of the immune system not only contribute to the pathology, but are also key regulators of heart function [15, 16], highlighting the role of immune system cells in heart homeostasis and the ability to respond and become activated.

Nowadays, despite the efforts, no pharmacological intervention introduced in the clinical guides to treat HF achieves direct modulation of the immune system with additional clinical benefits. Thus, unraveling the different immune pathways can help tackle a common player as a potential target. In this sense, inflammasome and B cell activation have demonstrated to play an important role in HF considering both inflammatory mechanisms activate during acute local inflammation [13, 17–20] and with associated risk factors, such as obesity and aging [21–23], which can contribute to low chronic systemic inflammation and declining heart function [24]. Some therapeutic strategies against both have already been tested in animal models and in a clinical context [17, 25, 26]. However, except for IL-1β, a resultant product of inflammasome activation [27, 28], none of them have been evaluated as possible targets in the different HF subclassifications. Here, we review the immunological pathways, both acute and chronic, that allow an inflammatory stimulus to persist and contribute to the development of HF, highlighting the common players in innate and adaptive immunity.

Inflammation Pathways in HF

HF can be sub-classified into three groups according to the ejection fraction (EF): ≥ 50% as HF with preserved ejection fraction (HFpEF), 40–49% as HF with mid-range EF (HFmrEF), and < 40% as HF with reduced ejection fraction (HFrEF) [29]. HFmrEF is more frequently observed in patients with coronary artery disease and responds similarly to treatments for HFrEF with resembling features [30, 31]. Thus, we are going to focus our attention on HFpEF and HFrEF. It has been suggested that HFrEF and HFpEF have distinct inflammatory features. Biomarkers measured in patients with ischemic and non-ischemic HF found that HFpEF was more associated with inflammatory markers, as opposed to HFrEF, which was more related to biomechanical cardiac stress markers such as BNP [32, 33]. In this regard, it has been postulated that HFpEF results from a chronic pro-inflammatory state induced by comorbid conditions such as obesity, hypertension, and diabetes, which triggers microvascular endothelial cell inflammation and stress oxidation, whereas HFrEF is mainly promoted by a direct cardiac insult as occurs in myocarditis or ischemia [34]. However, as a result of cardiac insults, molecular patterns associated to damage or pathogens (DAMPs and PAMPs, respectively) are generated and presented leading to inflammatory features that have been widely studied in patients with HFrEF, such as inflammatory innate/adaptive cells activation, cytokines, and autoantibodies against cardiac antigens; all of them associated with severity, poor prognosis, and rehospitalization [6, 7, 35, 36]. These studies have allowed the development of new therapeutic approaches by recognizing the role of immune cells, particularly adaptive immunity, as a key player in sustained inflammation and disease progression [19, 25]. Despite both types of HF having different triggers and cellular interplay, end-stage HF derived from either type share many etiology independent features. However, since the primary inflammatory mechanisms described are from studies on HFrEF, in both human and animal models, the role of inflammation in HFpEF remains to be clarified [35–37]. It is worth noting that many of the currently available therapies have shown improvements in the clinical outcomes of patients with HFpEF but not with HFrEF [30], an etiology with a rising prevalence [38]. A different pattern of circulating inflammatory cytokines was reported in rats with HFrEF (ligation of the left coronary artery) showing higher TNF-α plasma levels as opposed to HFpEF (high-salt diet) which demonstrated higher IL-1β and IL-12 levels [39]. Therefore, understanding the inflammatory process in both types of HF could allow us not only to unravel the differences, but also to suggest specific therapies for HFpEF instead of transposing them from HFrEF or even find a common player as a therapeutic target.

Cardiac Injury Activates Inflammatory Pathways

Cardiac acute local inflammation is a process with a vast array of causes; these vary from infectious, toxins [40], or myocardial infarction. Infectious inflammatory myocarditis may be associated with viruses, bacteria, fungal entities, or parasites. From these, viral myocarditis is of particular interest due to its progression to dilated cardiomyopathy (DCM) and HF [41]. From an inflammatory standpoint, most viral infections can be cleared without sequelae. However, some infections are associated with cardiomyocyte lysis after entering these cells and releasing self-antigens. Cardiomyocytes have a higher rate of being infected than fibroblasts, although the latter have higher replication rates [42]. After infection, the host mounts an inflammatory response through the production of several pro-inflammatory cytokines, such as IL-1α, IL-6, TNF-α, IFN-γ, and the activation of monocytes and NK cells, which induce apoptosis in infected cells [43]. As mentioned previously, viral myocarditis is linked to DCM, and although not well understood, in any cardiac inflammatory setting, there is a risk to develop chronicity, as has been recently shown by Groot and Hilde, from non-obstructive cardiovascular disease to ischemic HF [44]. The interplay of increased cytokines also skews T cells between Th1/Th2 and Th17/Treg responses [45, 46], each with specific inflammatory functions, yet all associated with chronic inflammation when skewed.
During an ischemic event, the neutrophils are the first cells to arrive and infiltrate the tissue, and it has been demonstrated that the basal levels can predict the progression to ischemic HF [44]. Once in the myocardium, influenced by the release of inflammatory cytokines, neutrophils activate and release a series of inflammatory mediators such as high levels of reactive oxygen species (ROS), IL-1β, myeloperoxidase, and proteases, which increase local tissue injury [47]. Of note, the increase in neutrophil counts and/or its ratios, such as neutrophil: lymphocytes and neutrophil: platelet ratio [48, 49], have demonstrated to have clinical relevance in stratifying a patient’s severity. This cytokine-mediated inflammation contributes to inflammatory loops and induces sub-acute and chronic inflammation [50]. Persistence of this inflammatory response causes additional secondary damage to the nearby tissue. There is also enough evidence of the effect of inflammation influencing the dysfunctional contractile state in HF, for example, by TNF-α [51]. Finally, some specific neutrophils can induce polarization of monocytes to a reparative phenotype, inducing a pathologic production of fibrosis [52].

The inflammatory response to the pathogens, infected cells, and damaged cells/tissues, which release DNA and ROS [20, 50], elicits the activation of pattern recognition receptors (PRR), such as toll-like receptors (TLRs) and nucleotide-binding and oligomerization domain- (NOD-) like receptors (NLRs) as NLRP3 (NOD-, LRR-) associated with the inflammasome. NLRP3 inflammasome activation results in IL-1β and IL-18 cytokine production, both related to cardiac dysfunction, reduced left ventricular contractility, worsening, and increased mortality [53, 54]. On the one hand, IL-1β promotes contractile dysfunction and secondary cytokine-induced damage [50, 54, 55]. In the cardiomyocytes, IL-1β promotes systolic dysfunction by altering mitochondrial function [56] and decreasing β-adrenergic responsiveness of L-type calcium channels and connexin 43 [57, 58]. On the other hand, IL-18 induces neutrophil accumulation and activation [59]. Recent evidence shows that after an inotropic stimulus, IL-18 is produced as early as 1 h and remains at 72 h, whereas IL-1β and TNF-α become expressed until 72 h of the stimulus [13]. Furthermore, β-adrenergic receptor (β-AR) activation seems to specifically induce IL-18 maturation in the heart but not in the spleen, lung, liver, or kidneys. These elevated levels of IL-18 were primarily detected in cardiomyocytes within the first hour and then in macrophages after 24 h [13], indicating that the inflammasome pathway is primarily driven by cardiomyocytes in response to neurohormonal activation. In turn, IL-18 induces β-adrenergic responsiveness that associates with LV dysfunction [60] and promotes BNP synthesis [61]. Therefore, targeting the inflammasome pathway has been suggested as an important therapeutic step as caspase-1 inhibition has demonstrated to have a protective effect on ischemia-induced human myocardial dysfunction through inhibition of the IL-18 and IL-1β processing [26, 60, 62]. An example of this is 16673-34-0 (5-chloro-2-methoxy-N-[2-(4-sulfamoylphenyl) ethyl]benzamide), an intermediate substrate free of the glyburide synthesis, which has shown benefits in ischemia-reperfusion animal models by reducing the infarct area without affecting glucose consumption and metabolism [63, 64]. The activation of the inflammasome pathways through IL-18 contributes with adaptive immunity regulation and thus with long-term responses by B and T cells, specifically favoring Th1/Th2 imbalance by the activation of Th1 cells and by modulating Th2 and Th17 responses [60]. The IL-18/IL-12 axis is considered the master controller of the Th1 response, giving a rise in the high level of production of IFN-γ, which also enhances B cell response [65, 66], including maturation and isotype switching [67, 68]. Hence, inflammasome activation seems to play an important role as a bridging pathway between innate and adaptive responses that contribute to HF development.

The risk of chronic inflammation to become systemic is also closely related to the induction of an autoimmune scenario, where the initial damage of the tissue is associated with the presentation of an antigen or a similar self-antigen, thereby initiating the damage modulated by CD4 cells and promoted by CD8 cytotoxic cells by its perforin, granzyme, and FAS-mediated apoptosis induction mechanism. Alongside the effects of T cells, B cells have an active and critical role in the development of HF remodeling and dysfunction [7, 17–19], either by modulating inflammatory cell recruitment [16, 18] or by increasing the inflammatory response through the production of autoantibodies [7] and fibrosis [19]. Moreover, interfering T cell co-stimulation by antigen presenting cell (dendritic cell, macrophages, and B cells) attenuates heart dysfunction mediated by IL-10-producing B cells [69].

An overview of the general immune players in the development of HFrEF is shown in Fig. 1.

The Heart as a Target of Systemic Inflammation

Chronic systemic inflammation induced by conditions such as obesity, hypertension, autoimmunity, and aging increases the risk to develop CVD and progress to HF [10, 70, 71]. Despite, the current understanding about the progression to HF, gleaned by the knowledge of the inflammatory pathways that are induced in these conditions, a recent mouse model, consisting of a combination of a high-fat diet (HFD) plus L-NAME has demonstrated a resemblance with human HFrEF pathophysiology since 5 weeks of treatment that remained until a year of follow-up [72•]. This model elicited a systemic proinflammatory state and, therefore, may provide a useful tool in understanding the inflammatory process that leads to HF and, in turn, to determine the immune features that play a critical role in HF development and to propose or test new therapeutic strategies for patients with HFrEF. Although previous animal models of HFrEF were established with rats [73,
Despite the aforementioned, it is well recognized that chronic systemic inflammation is the keystone player in HFpEF by promoting coronary microvascular endothelial inflammation, oxidative stress, lowering nitric oxide, and cardiomyocytes loss [77]. Furthermore, inflammatory mediators can induce direct activation in cardiac resident immune cells, such as macrophages and B cells, which also contribute to normal cardiac function [15, 16] and regulate the traffic of immune cells [16**]. Therefore, B cells may be responsible for monocyte infiltration, as observed in a myocardial infarction model [18], and also contribute to cardiac dysfunction in a non-classical way.

In obesity, local inflammation in adipose tissue induces innate and adaptive cell infiltration promoting a low-grade chronic systemic inflammatory state that involves the secretion of proinflammatory cytokines, adipokines, and IgG immunoglobulins [78, 79]. We recently demonstrated that significant weight loss after bariatric surgery results in systemic inflammation markers such as normalization of CRP levels, decreases in the B cell activation factors, and inflammasome activation byproducts (unpublished data). The decreased inflammation by bariatric surgery-induced weight loss reduces CVD risk [80].

Animal models with obesity display mitochondrial hyperacetylation, fragmentation, ROS production, and mitochondrial permeability transition pore openings with diastolic dysfunction [81–83]. All these changes contribute to...
mitochondrial DNA (mtDNA) release and systemic inflammation [84] that, in conjunction with ROS, are inflammasome activators involved in heart inflammation [85]. As a result, IL-18 secretion may induce fibrosis and cardiac hypertrophy resulting in diastolic stiffness [86] and concentric remodeling [87], whereas IL-1β can induce diastolic dysfunction by altering calcium handling, decreasing the expression of SERCA (sarcoplasmic reticulum calcium ATPase), and phospholamban (PLB) and, therefore, calcium recaptured [56].

As well as in obesity, hypertension, and aging also contribute to HF that involves systemic oxidative stress and inflammation [88–90], which leads to a coronary microvascular endothelial dysfunction [91] with fibroblast proliferation associated with the decrease in NO [92] and diastolic dysfunction [75]. Furthermore, inflammasome-genesexpression associated with chronic inflammation and mortality was linked with IL-1β, oxidative stress, and nucleotide metabolism dysfunction [12]. With this, NLRP3 inflammasome may be considered as a clinical target in HFpEF (Fig. 2).

Autoimmunity is widely recognized as a CV risk factor that correlates with the duration of the disease and mortality risk as a result of chronic systemic inflammation [70, 93–95]. Other supporting data that indicates that systemic inflammation is an important associated mechanism is that the acute systemic inflammation occurring after infections, as is the case of SARS-CoV virus, increases the risk of CVD and more associated event years after the disease resolution [96]. This suggests that acute systemic inflammation can “prime” cells of the immune system in the heart and make them more prompt to become activated and develop HF. Therefore, patients that currently course with a SARS-CoV-2 infection, associated with a cytokine storm [97], might have acquired an additional risk factor to developed CVD and HF.

Fig. 2  Role of systemic chronic inflammation in the development of HF: from systemic to heart inflammation. There is direct modulation of inflammatory diseases and cellular events like obesity in TLR and NLRP3 inflammasome activation. The inflammatory cytokines alongside DAMPs, and the combination of both the innate and adaptive immune system activation affect the vascular endothelium cells. Therefore, this has an impact in the cardiomyocyte. This continuous inflammatory loop allows for pathologic damage, increasing the production of more inflammatory cytokines and DAMP mediators such as ROS. These events lead to immune cell shifts, pathologic tissue remodeling, hypertrophy, dysfunction, and continuous inflammatory cell signaling. IL, interleukin; IFN, interferon; NO, nitric oxide; TLR, toll-like receptors; TNF, tumor necrosis factor; ROS, reactive oxygen species; mt-DNA, mitochondrial DNA; mt-ROS, mitochondrial reactive oxygen species.
Table 1  Clinical trials that directly target IL-1β, as inflammasome component, or B cells

| Target | Clinical trial ID | Clinical trial phase | Study | Drug | Year | Number of patients | Time of treatment | NYHA class | Primary endpoint | Primary endpoint reached? | Other outcomes | Author |
|--------|-------------------|----------------------|-------|------|------|-------------------|-------------------|------------|-----------------|---------------------------|---------------|--------|
| IL-1β  | NCT01936909       | III                  | RED-HART | Anakinra | 2013 | 60 | 12 weeks | II-III | Peak oxygen consumption | Yes | Decreased incidence of death/hospitalization | Van Tassell [99] |
|       | NCT01175018       | II                   | VCU-ART2 | Anakinra | 2010 | 30 | 2 weeks | III-IV | Change in left ventricular end-systolic volume | Yes | Abbate [100] |
|       | NCT01327846       | III                  | CANTOS  | Canakinumab | 2011 | 10066 | 2 weeks | II-III | Safety | Yes | Glynn [101] |
|       | NCT01936844       | III                  | Anakinra | Anakinra | 2013 | 30 | 2 weeks | II-III | Reduction in inflammatory marker CRP | Yes | Van Tassell [102] |
|       | NCT01900600       | NA                   | D-HART substudy | Canakinumab | 2013 | 15 | 12 weeks | II-III | Peak oxygen consumption | Yes | LVEF improvement | Trankle [103] |
|       | NCT02547766       | II                   | — | Anakinra | 2015 | 10 | 2 weeks | IV | Reduction in inflammatory marker CRP | Yes | Selzman [104] |
| HFrEF  | NCT01542502       | NA                   | D-HART Pilot Study | Anakinra | 2012 | 12 | 2 weeks | II-III | Peak oxygen consumption | Yes | CRP and leukocyte count | Van Tassell [105] |
|       | NCT02173548       | II                   | D-HART2 | Anakinra | 2017 | 31 | 12 weeks | II-III | Cardiorespiratory fitness | No | hs-CRP and NT-proBNP | Van Tassell [28] |
| B cells | NCT03332888       | II                   | ICFEr-RITU2 | Rituximab | 2017 | 10 | 6 months | III-IV | Emergent Cardiovascular Adverse Events | | Sánchez-Trujillo [25] |
Table 2  Clinical trials associated to other immunomodulatory strategies

| Target ID | Clinical trial Study | Drug                          | Year | Number of patients | Time of treatment | NYHA class | Primary endpoint | Primary endpoint reached? | Status       | Author                  |
|-----------|----------------------|-------------------------------|------|--------------------|-------------------|------------|------------------|--------------------------|--------------|-------------------------|
| TNF-α     | HFrEF                | ATTACH Infliximab             | 2003 | 150                | 14 weeks          | III-IV     | Safety           | No                       | Complete     | Chung [122]             |
|           |                      | RENEWAL: RECOVER & RENAISSANCE |      |                    |                   |            |                  |                          |              |                         |
|           | Broad spectrum immunomodulation | HELPER: Cannabidiol | 2018 | 20                 | 6 months          |            | Adverse events   |                          | Not yet recruiting | Jerjes-Sánchez [124] |
|           |                      | Resveratrol                  | 2013 | 40                 | 12 months         | II-III     | Quality of life  |                          | Recruiting   | Malik [125]            |
|           |                      | Pentoxifylline               | 2011 | 45                 | 6 months          | II-III     | LVED improvement |                          | Unknown      | Ananthasubramaniam [126] |
|           |                      | Pentoxifylline               | 2020 | 50                 | IV                |            | Reduction in REBC hemolysis |                          | Not yet recruiting | Emerson [127]         |
|           |                      | Colchicine                   | 2015 | 4745               | 22.6 months       | MI          | Adverse cardiovascular events | Yes                      | Complete     | Tardif [128]           |
|           |                      | Colchicine                   | 2014 | 279                | 6 months          | II-III     | NYHA improvement | No                       | Complete     | Deftereos [129]        |
|           |                      | Methotrexate                 | 2008 | 50                 | 12 weeks          | II-IV      | difference in 6-min walk test | No                       | Complete     | Moreira [130]          |
|           |                      | Thalidomide                  | 2012 | 100                |                   | III-IV     | Changes in left ventricular ejection fraction |                          | Unknown      | Pelliccia [131]        |
|           |                      | Umbilical cord mesenchymal stem cells | 2012 | 30                 | 12 months         | I-III      | NYHA improvement | Yes                      | complete     | Bartolucci [132]       |
|           |                      | n-3 PUFAs                    | 2010 | 133                | 12 months         | II-III     | Left ventricular function | Yes                      | Complete     | Nodari [133]           |
|           |                      | Intravenous immune globulin  | 2001 | 62                 | 12 months         | I-IV       | Left ventricular function | Yes                      | Complete     | McNamara [134]         |
|           |                      | Immune activation-autologous blood exposed to stress | 2005 | 75                 | 6 months          | I-IV       | NYHA classification, mortality and hospitalization risk | Yes                      | Complete     | Torre-Amione [135]     |
| HFrEF     |                      | GRAPEVINE-HF                 | 2010 | 15                 | 6 weeks           | II-III     | Brachial artery flow | Complete | Hummel [136]          |
| HFrEF and HFrEF |                | Resveratrol                  | 2018 | 40                 | 8 weeks           | II-III     | Brachial artery flow | Recruiting | Ezekowitz [137]        |
## Targets for Therapeutic Intervention

### Inflammasome Activation (Innate Immunity)

Therapies associated with blocking the NLRP3 inflammasome have yielded promising results. An example of this, as previously mentioned, is the glyburide analog, 16673-34-0, that has shown benefits in ischemia-reperfusion animal models [63, 64, 98]. Although no clinical trials are being conducted to target NLRP3 directly, IL-1β, a byproduct resulting from NLRP3 activation, has revealed beneficial outcomes associated to inflammation resolution in both HFrEF and HFpEF. Several clinical trials (Table 1) [27, 28, 99, 106] have shown a risk reduction in nonfatal stroke or cardiovascular death alongside hospitalization of unstable angina after myocardial infarction [27••] as well as in patients with end-stage acute decompenated heart failure [102] with early positive results regarding aerobic capacity and ventilatory efficiency [99]. In infectious and septic myocarditis, they have shown positive effects of improvement and recovery [107, 108]. Moreover, patients with rheumatoid arthritis receiving this therapy reveal improvement in LVEF and LVESVi [109, 110]. Regarding HFpEF, a reduction of ongoing inflammation and cardiac stress biomarkers (high-sensitivity-CRP and NT-pro-BNP, respectively) was observed but with opposing results regarding aerobic capacity that was the primary goal of the study [28] and was previously observed in a pilot study [105]. As investigators point out, this discrepancy might be associated with the greater grade of obesity in the second study which alters the aerobic capacity by its own condition (median body mass index = 42) [28]. Additionally, IL-18 secretion is not altered by IL-1β inhibition [111] and as we mentioned before, IL-18 is primary secreted by the cardiomyocytes [13] and is also important during chronic inflammation as occurred in obesity [112]. Thus, clinical trials targeting inflammasome might be promising.

### B Cells (Adaptive Immunity)

B cell activation plays a central role leading to chronic and systemic inflammation as observed by the increase presence of serum/plasma immunoglobulins, either intact or as a free light chains in patients with HF [113, 114] and associated comorbidities [79, 115]. Moreover, the presence of anti-cardiac antibodies in failing heart biopsies demonstrates their relevance in cardiac dysfunction [7, 113]. In this context, therapeutic plasma exchange performed in patients with HFrEF with NYHA functional class II–IV not only improved cardiac function but also showed less IgG cardiac deposition after 6 months of treatment [116]. Notably, recent data in a murine model demonstrates that B cell subpopulations (CD19⁺CD11b⁺⁺) have a specific patrolling role in the heart with functional relevance, by regulating other immune cell

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### Table 2 (continued)

| Target | Clinical trial ID | Study Drug | Year | Number of patients | Time of treatment | NYHA class | Primary endpoint | Primary endpoint reached? | Status | Author |
|--------|-------------------|------------|------|--------------------|------------------|------------|------------------|---------------------------|--------|--------|

**Change in isolated skeletal muscle blood flow and oxygen consumption**
trafficking and heart function [16••]. In fact, CD19+CD11b− B cells are associated with cardiac fibrosis [19], which is in line with data for depleting B cells that indicates that B cells are involved in fibrosis, heart dysfunction, and hypertension [17, 18, 117].

Although these findings are difficult to study on heart biopsies under physiological conditions, B cells were observed in close contact with the cardiac endothelium and, to a lesser extent, in the myocardium in failing heart biopsies [16••]. Indeed, in patients, the uses of rituximab—a selective CD20-B cells depleting antibody—showed clinical improvement [118]. Ongoing phase I/II clinical trials in patients with HFrEF and an acute ST segment elevation myocardial infarction were recently submitted (Table 1) [36, 119] but none of them involved patients with HFpEF. Detailed information regarding B cell mechanism involved in HF and targeting approaches has been recently reviewed [120].

**Other Strategies Targeting Immune System**

After the TNF-α clinical trials (previously reviewed) [121–123], multiple therapies have been postulated using mostly broad spectrum immunomodulators. However, most have been tested mainly on patients with HFrEF (Table 2). Recently, molecules with anti-inflammatory and antioxidative properties have gained some attention such as resveratrol and cannabidiol (CBD) with recent ongoing clinical trials [124]. The potential of these molecules to be effective at targeting both, HFrEF and HFpEF, relies on the fact that in both conditions, mitochondrial dysfunction and ROS production are associated with cardiomyocytes cell death, DAMPs released (inflammation), and ultimately HF (Fig. 3) [81, 82, 138]. For instance, CBD directly reduces mitochondrial oxidative stress and cardiomyocyte hypertrophy (in vitro) and impairs cardiac remodeling and systemic inflammation in a model of HF with systolic dysfunction [139].

Other molecules that have shown immunomodulation properties with ongoing clinical trials are pentoxifylline, colchicine, statins, methotrexate, thalidomide, and allopurinol, among others. Pentoxifylline is a methylxanthine derivative that has demonstrated the capacity to interfere with TLR and inflammasome signaling pathways, as well as with the expression of CD80 costimulation molecule [140]. Sequentially, the impaired danger signals recognition and APC-T cell costimulation results in clinical improvement in patients with HFrEF and could potentially be beneficial for HFpEF due to the involved mechanisms [141, 142]. In this context, colchicine, which inhibits microtubule polymerization, interferes with NLRP3 activation and thus IL-1β and IL-18 secretion. However, this effect only showed decreased inflammatory biomarkers without changes in the clinical outcomes in patients with HFrEF treated for 6 months [129]. Nonetheless, a larger clinical trial with a follow-up of more than 20 months found that colchicine treatment lowered the risk of ischemic cardiovascular events [128]. On the contrary, statins, which seem to modulate the inflammatory response by restoring NO and endothelial function [143] which is the primary inflammatory pathway described in HFpEF patients, did not demonstrate any effect in chronic HF, independent of NYHA.
functional class, and left ventricular ejection fraction [144]. This suggests that once chronic inflammation is established, alleviating endothelial dysfunction is not enough to rectify the inflammatory loop. Studies with methotrexate, thalidomide, and allopurinol showed neutral results, in small sized clinical trials (Table 2).

Conclusions

It has already been proposed that the cross-talk between heart and peripheral tissues may be importantly mediated by NLRP3 inflammasome [145]. NLRP3 activation is strongly associated with the oxidative stress that occurs in both kinds of damage in cardiomyocytes, acute local [138, 146], and chronic systemic inflammation [81, 82]. This could explain why blocking IL-1β has shown promising results in both HFrEF and HFP EF [27, 28]. Given that IL-18 seems to play an essential role in both etiologies, targeting inflammasome may provide further beneficial outcomes. Furthermore, recent findings have shown that IL-1β/NLRP3 pathway associates with age-related hematopoietic stem cells clonal expansion that associates with increased CVD risk and all-cause mortality [147]. On the other hand, adaptive immunity is fundamental to sustain and establish a higher affinity and quicker response to the original stimuli by generating memory. In this context, B cells stand out because they can directly recognize the antigen, modulate other immune cells (T cells, monocytes), and release cytokines and antibodies that modulate the inflammatory response. This approach has already been testing in HFrEF [25, 118] but not in HFP EF. Given that the cellular immune system can help predict CVD mortality [11], knowing precise subpopulations may provide the opportunity to establish the right anti-inflammatory strategy depending on the ongoing inflammatory response. Lessons learned from current clinical trials, not only for HF but also in other pathologies that target common immune characteristics present in heart failure or that have demonstrated positive effects on heart function as occurs in patients with autoimmune diseases, could help to translate these findings into therapeutic strategies for patients with HF. For example, protocols with rituximab have demonstrated that patients with elevated pre-switch memory B cells (CD19+ IgD+ CD27 + CD95−) associate with adverse outcomes [148]. Therefore, immunotyping B cells in heart failure patients could avoid these effects.

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Data Availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with Ethical Standards

Conflicts of Interest Gerardo Garcia-Rivas and Guillermo Torre-Amione are co-founders of Nano4Heart, a start-up company focused on developing immunotherapies for the treatment of heart failure. The other authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of major importance

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