The Immune System and Chronic Heart Failure

Is the Heart in Control?

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Despite current treatment options, the clinical course of patients with chronic heart failure is notoriously difficult to predict. Among those with similar etiologies, ejection fractions, and patient demographics, our understanding of why such variations in outcomes exist remains limited. Evidence that has been progressively gathered implicates an important role of the immune system in the propagation of heart failure. This has been derived mainly from observations that cytokines are progressively elevated in patients with poor outcomes. However, attempts at introducing various immunomodulatory therapies as a new treatment strategy have been largely unsuccessful to date. This possibly reflects a failure in recognizing the complexity of the immune system’s role in chronic heart failure, which has led to an oversimplified approach to treatment. This review critically analyzes the immune treatments attempted to date and hypothesizes what is required to develop a successful future treatment strategy. (J Am Coll Cardiol 2009;53:1013–20) © 2009 by the American College of Cardiology Foundation

Following reports that serum tumor necrosis factor (TNF)-alpha concentrations are elevated in patients with severe chronic heart failure (CHF) (1), an appreciable research effort has attempted to describe the role of the immune system in the disease. Many studies have reported elevated levels of both inflammatory and anti-inflammatory cytokines, together with their corresponding receptors in CHF (2,3). This has led researchers to attempt to address the role of immune cells in the disease, with many contradictory findings (4–6). However, despite an unclear role for the immune system in CHF, the utilization of novel immunomodulatory treatment modalities has been attempted in humans, with indifferent results (summarized in Table 1).

Attempts at Immunomodulatory Therapy in CHF

The largest trial of anti–TNF-alpha therapy in humans was the RENEWAL (Randomized Etanercept Worldwide Evaluation) (RENAISSANCE [Randomized Etanercept North American Strategy to Study Antagonism of Cytokines] and RECOVER [Research Into Etanercept Cytokine Antagonism in Ventricular Dysfunction]) trial (7). This international multicenter study of 1,500 heart failure patients with New York Heart Association (NYHA) functional class II to IV was prematurely terminated as it failed to demonstrate an advantage of treatment with etanercept (a recombinant deoxyribonucleic acid protein that binds to the human TNF-alpha receptors via the crystallizable fragment components of immunoglobulin subclass immunoglobulin G1). The study investigators provided 3 putative explanations as to why TNF-alpha inhibition had no clinical benefit to human heart failure (including the concept that proinflammatory cytokines are not involved in CHF, that the dose of etanercept was not sufficient to adequately inhibit TNF-alpha function, or that the “targeted” approach used in this study could not disrupt inflammatory processes). Another theory that might explain the results of the RENEWAL trial is that TNF-alpha is a pleiotropic cytokine involved in many physiologic and pathologic processes, some of which are involved in cardioprotective pathways. For example, TNF-alpha provides endogenous cytoprotective signals that prevent cardiomyocyte apoptosis following ischemic injury (8). Furthermore, the absence of TNF type 1 receptors has been associated with larger myocardial infarction in mice exposed to coronary artery occlusions (9). In the same models, TNF type 1 receptor deficiency was also associated with accelerated myocardial death (described as an apoptotic or induced process, rather than necrosis).

The findings of a smaller clinical trial (n = 150) using the chimeric monoclonal TNF-alpha antibody, infliximab, in a cohort of patients with moderate/severe heart failure provided further evidence of a myocardial requirement for TNF-alpha (10). In this study, patients were grouped as placebo (n = 49), 5 mg/kg infliximab (n = 50), or 10 mg/kg infliximab (n = 51) and followed up at 14 and 28 weeks. The investigators reported that patients on high-dose infliximab were more likely to experience deterioration in clinical status at both of these time points. Indeed, this group was at a higher risk of major adverse events including...
hospitalization as a result of heart failure and death (hazard ratio: 2.84, \( p < 0.05 \)). Patients were followed up for a further 5 months following study closure, and again the investigators reported that the patient group that had received high-dose infliximab continued to have a worse clinical outcome than the other treatment groups. In this study, both infliximab treatment groups were associated with a rapid decrease in serum TNF-alpha, followed by an increase in concentration (above baseline values) at all other time points over the 28-week study period. The investigators suggested that TNF-alpha secretion was increased as a result of antibody treatment, explaining the poor clinical outcome in the high dose infliximab group. This would conflict with the concept that TNF-alpha is required for myocyte homeostasis and prevention of myocyte death. Yet, this would not explain the difference in clinical outcome between the 5-mg/kg versus 10-mg/kg treatment groups. Moreover, the investigators could not detect biologically active TNF-alpha in the samples, suggesting that the elevated TNF-alpha levels were biologically inactive, TNF-alpha–infliximab complexes. Another theory offered was that infliximab might potentiate cardiac toxicity of TNF-alpha by forming these TNF-alpha–infliximab complexes, which retain TNF-alpha in the circulation, prolonging TNF-alpha exposure. This argument seems "immunologically" flawed because although we clearly do not understand the positive or negative roles of TNF-alpha in CHF, any effect TNF-alpha may have on the myocardium will be at the cellular/tissue level, rather than a circulating, systemic mechanism of action.

Other agents have also been identified as potential therapeutic tools for CHF because of their capacity to inhibit TNF-alpha, including the glutamic acid derivative, thalidomide (11). Thalidomide reportedly induces the degradation of TNF-alpha messenger ribonucleic acid transcripts, preventing the accumulation of TNF-alpha messenger ribonucleic acid and therefore protein production (12). Two very small trials (both \( n = 7 \)) and 1 small placebo-controlled study (\( n = 56 \)) (13,14) have reported that thalidomide treatment is associated with an improvement in left ventricular ejection fraction (LVEF). However, contrary to this, a further study of 80 patients with heart failure reported no effect of thalidomide on LVEF (15). The multifarious effects of thalidomide on the immune system may explain these contradictory findings. For example, thalidomide inhibits activation of the promoter for the TNF-alpha transcription factor, nuclear factor kappa B, but only in monocytes. This has been further defined as thalidomide prevents TNF-alpha secretion by monocytes following lipopolysaccharide stimulation. However, these effects appear exclusive to monocytes and are not replicable in T cell populations. Indeed, the effects of thalidomide on T cells appear entirely different. T cells that express the CD4+ and CD8+ markers proliferate and secrete inflammatory cytokines (including interleukin [IL]-2 and interferon-gamma) in response to thalidomide treatment, via costimulation. This costimulatory process has been demonstrated to induce TNF-alpha synthesis (in an IL-2-dependent manner) by CD4+ and CD8+ T cells (16).

### Table 1 Summary of Clinical Trials Attempting the Use of Immunomodulatory Agents in the Treatment of CHF

<table>
<thead>
<tr>
<th>Author (Ref. #)</th>
<th>Agent</th>
<th>Target</th>
<th>n</th>
<th>Outcome (+/-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mann et al. (7)</td>
<td>Etanercept</td>
<td>TNF-alpha</td>
<td>1,500</td>
<td>(study terminated early due to lack of advantage)</td>
</tr>
<tr>
<td>Chung et al. (10)</td>
<td>Infliximab</td>
<td>TNF-alpha</td>
<td>150</td>
<td>(infliximab associated with worse outcome)</td>
</tr>
<tr>
<td>Agoston et al. (13)</td>
<td>Thalidomide</td>
<td>Multiple modes of action</td>
<td>7</td>
<td>(improvement in LVEF)</td>
</tr>
<tr>
<td>Gulstedt et al. (14)</td>
<td>Thalidomide</td>
<td>Multiple modes of action</td>
<td>56</td>
<td>(improvement in LVEF)</td>
</tr>
<tr>
<td>Orea-Tejeda et al. (15)</td>
<td>Thalidomide</td>
<td>Multiple modes of action</td>
<td>80</td>
<td>(no beneficial effect reported)</td>
</tr>
<tr>
<td>Silwa et al. (18)</td>
<td>Pentoxifylline</td>
<td>Multiple modes of action</td>
<td>28</td>
<td>(improvement in NYHA functional class and LVEF, decrease in TNF-alpha)</td>
</tr>
<tr>
<td>Skudicky et al. (19)</td>
<td>Pentoxifylline</td>
<td>Multiple modes of action</td>
<td>49</td>
<td>(improvement in NYHA functional class and LVEF, decrease in TNF-alpha)</td>
</tr>
<tr>
<td>Bahrmann et al. (20)</td>
<td>Pentoxifylline</td>
<td>Multiple modes of action</td>
<td>47</td>
<td>(no improvement in NYHA functional class and LVEF, decrease in TNF-alpha)</td>
</tr>
<tr>
<td>Pugh et al. (22)</td>
<td>Testosterone</td>
<td>Suppression of proinflammatory cytokines</td>
<td>12</td>
<td>(improvement in NYHA functional class)</td>
</tr>
<tr>
<td>Torre-Amione et al. (24)</td>
<td>Intragluteal injection apoptotic autologous blood</td>
<td>Nonspecific immunomodulation</td>
<td>2,426</td>
<td>+/- (primary end point not met, although beneficial effect reported in NYHA functional class II)</td>
</tr>
<tr>
<td>Gulstedt et al. (33)</td>
<td>Octogam (immunoglobulin)</td>
<td>Multiple modes of action</td>
<td>40</td>
<td>(improvement in LVEF)</td>
</tr>
<tr>
<td>Aukrust et al. (34)</td>
<td>Octogam (immunoglobulin)</td>
<td>Multiple modes of action</td>
<td>39</td>
<td>(improvement in LVEF, complement activation)</td>
</tr>
</tbody>
</table>

CHF = chronic heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; TNF = tumor necrosis factor.
induces the up-regulation of CD40L (CD154) expression on CD8+ T cells, which will protract CD8+ T cell lifespan and also instigate activation of CD40+ dendritic cells (DCs). Thalidomide also has litigious effects on TNF-alpha in the clinical setting. Several reports have demonstrated a reduction in serum TNF-alpha concentration following treatment (7), yet others, including heart failure studies, have failed to show any difference or have actually demonstrated that thalidomide treatment induces an increase in TNF-alpha (14).

Other attempts at therapeutic TNF-alpha modulation have also been reported, including treatment with the xanthine derivative pentoxifylline, which exerts peripheral vasodilatory effects, improves blood hemodynamics, and is reported to reduce serum TNF-alpha (17). The work by Sliwa et al. (18) and Skudicky et al. (19) demonstrated that treatment with pentoxifylline is associated with a significant improvement in NYHA functional class and LVEF, along with a decrease in circulating TNF-alpha (initially in 28 patients with idiopathic dilated cardiomyopathy) and Fas (described in a follow-up report of 49 patients). However, the investigators found that alternations to TNF-alpha concentration did not directly correlate with LVEF or NYHA functional class improvement and that TNF-alpha did not represent an independent predictor of outcome in this small cohort. This suggests that the beneficial effects of pentoxifylline treatment are independent of TNF-alpha, implying TNF-alpha depletion is a consequence rather than a cause of cardiac improvement. To add further controversy to the effects of pentoxifylline, a study by Bahrmann et al. (20) attempted to replicate the Sliwa et al. (18) findings (in 47 patients) without any success. Assessment parameters included LVEF, NYHA functional class, and biomarker levels such as B-type natriuretic peptide, IL-6, and TNF-alpha. The thalidomide and pentoxifylline studies suggest our understanding of the immune response in heart failure requires further explication.

There have also been reports that low levels of androgens (which have been associated with CHF) may be responsible for increased concentrations of proinflammatory cytokines (such as TNF-alpha) in CHF patients. In vitro studies have demonstrated that testosterone down-regulates proinflammatory cytokine production (including IL-1-beta, IL-6, and TNF-alpha) from a range of cells (reviewed in [21]), and clinical trials using physiological testosterone therapy have reported improvements in NYHA functional class and exercise capacity of patients with CHF (22). However, recent evidence suggests the in vitro and in vivo data are not linked. In a placebo-controlled trial (n = 94), CHF patients treated with testosterone when compared with a control group were shown to have similar circulating TNF-alpha concentrations, suggesting the beneficial effects of testosterone therapy are TNF-alpha-independent (23).

Despite this clear lack of immune understanding, a clinical trial (24) attempted to induce “nonspecific immunomodulation” in a cohort of 2,426 patients with NYHA functional class II to IV heart failure (24). In this study, the investigators proposed that the intragluteal injection of autologous blood exposed to stress (ex vivo) would result in nonspecific immunomodulation in patients with CHF and thereby offer clinical benefits. The results failed to reach significance for the combined primary end point of time to death from any cause or first hospitalization for cardiovascular reasons. However, in 2 subgroups of those without previous myocardial infarction and of those with NYHA functional class II CHF, the primary end point was met. It was therefore suggested that the treatment might have a role in a large segment of the CHF population. However, the proposal that CHF patients with NYHA functional class II heart failure should benefit from immunomodulatory therapy above those with more severe grades (III and IV) seems counterintuitive. To date, it appears that heightened states of immune activation correlate with more severe grades of heart failure (4). If a pathogenic role of the immune system in this setting is acknowledged, it would seem logical that those with more severe NYHA functional classes would therefore stand to benefit the most. In the ACCLAIM (Advanced Chronic Heart Failure Clinical Assessment of Immune Modulation Therapy) study, NYHA functional class II patients only accounted for 30% and 27% of the active and placebo groups, respectively, which may impact on the statistical powering behind the otherwise significant result. Similar proportions were seen for the other subgroup, those with nonschemic CHF, gaining statistical significance. More importantly, however, the central tenet behind this particular study design was immunologically naïve. The immune system is a sophisticated and highly regulated orchestration of cellular and subcellular mechanisms, which leads to a localized response at a target area. The hypothesis that a small volume (10 ml) of autologous, apoptotic leukocytes injected into the gluteus maximus would systemically skew the immune response from inflammatory to anti-inflammatory seems unlikely. The investigators based their theory on in vitro work that reports that the immune system secretes anti-inflammatory cytokines following interaction with apoptotic cells and that apoptosis is the main form of myocyte death after coronary occlusion (25). Yet, sophisticated analysis of cardiomyocytes undergoing cell death has demonstrated that apoptosis pathways are not responsible, but oncosis, or cell death accompanied by swelling (rather than cell shrinkage seen in apoptosis), could be (26). Furthermore, apoptosis (which is a routine cellular event) occurs between 50 and 70 billion times per day, without any immunomodulatory effects. More specifically to the immune system, apoptosis acts as a tissue-signaling mechanism. For example, lymphocyte apoptosis occurs during propriocidal regulation (27), via TNF-alpha induction (where TNF-alpha is anchored to the leukocyte surface, which is then bound by a TNF receptor, inducing a death signal) (28), or during passive withdrawal (via IL-2 depletion when antigen is no longer present) (29). These natural and regulatory forms of apoptosis are not associated...
with a skewed anti-inflammatory response. When stress is induced via increased temperature, cells undergo "abnormal" cell death, rather than programmed cell death. In such circumstances, stress proteins are known to up-regulate. These include heat shock proteins and heme-1-oxygenase, which are known stimulators of antigen-presenting cells (APCs) such as DCs (reviewed in Srivastava [30]). However, DC responses to such stress proteins are not committed to anti-inflammatory pathways. Antigen-presenting cells also recognize intracellular proteins, which upon secretion (following cell death) induce localized, inflammatory (rather than anti-inflammatory) responses (reviewed in Matzinger [31]). Stress protein recognition is not restricted to APCs. Many innate cells (including natural killer cells) have been shown to activate and secrete inflammatory cytokines following stress protein recognition [23] (the investigators acknowledge reports describing immunomodulation of macrophages following heat shock protein stimulation [32]).

These issues are directly applicable to the ACCLAIM study, where cell stress was rapidly induced via ultraviolet exposure and oxidative stress following treatment with an anticoagulant. Therefore, the physiological response of the recipient immune system to such apoptotic cells is likely to increase inflammatory cytokine production, rather than impair it.

Two clinical trials, Gullestad et al. (33) and Aukrust et al. (34), reported beneficial effects of immunoglobulin treatment in patients with CHF and postulated a role for complement, and complement therapy. In the first study (33), a cohort of (n = 40) chronic, stable CHF patients with NYHA functional class II/III and an LVEF <40% were treated with a human-derived intravenous immunoglobulin (Octagam, Octopharma Ltd., Roselands, New South Wales, Australia) and compared with a placebo-controlled group (n = 20) over a 26-week period. Key markers including TNF-alpha, IL-1-beta, IL-10, soluble tumor necrosis factor receptor (sTNFR) p55, sTNFR p75, IL-1R-alpha, and N-terminal part of the pro-atrial natriuretic peptide were quantified, and any change in clinical outcome was described. A rise in IL-1R-alpha, IL-10, sTNFR p55, and sTNFR p75 was reported, in addition to an improvement in LVEF (26% to 31%, p ≤ 0.001) in the immunoglobulin-treated group. The changes observed in IL-1R-alpha, IL-10, sTNFR p55, and sTNFR p75 directly correlated with improved EF, suggesting a direct link between these molecules and myocardial function. The investigators also reported that the N-terminal part of the pro-atrial natriuretic peptide was decreased following immunoglobulin treatment, suggesting an improvement in hemodynamic status. As a result, it was concluded that "inflammatory mediators" are involved in the pathogenesis of CHF. Yet the mechanisms and immune processes behind these findings are very interesting and may be of use in identifying novel approaches to immunomodulation for CHF. Immunoglobulins are multifunctional, interacting with several mechanisms. For example, they are known to prevent immune cell–target cell (myocyte) interactions via a series of processes, including crystallizable fragment receptor blockade and competitive inhibition of antibody-dependent cellular cytotoxicity [35]. Furthermore, immunoglobulins are known to prevent cell death cascades, which in turn would prevent the expression and/or secretion of endogenous stress signals. Endogenous stress signals are essential for activation of innate cells, including myeloid dendritic cells and monocytes, and effector (target cell killing) cells, including natural killer cells and macrophages (which will be discussed in greater detail). In the second study, Aukrust et al. (34), an attempt was made to delineate the effect of immunoglobulin treatment on circulating complement factors in patients with CHF (n = 39) versus a healthy, untreated control population (n = 20). Complement was found to be elevated in patients with CHF when compared with controls, and interestingly, these levels (specifically C3bBbP, C3bc, and TCC) increased further following treatment with immunoglobulin. As a result, it was concluded that immunoglobulin treatment, although beneficial in improving LVEF, was associated with systemic complement activation. However, systemic complement activation does not represent an increase in localized complement deposition, so clearly further work is required. It would be interesting to study the effects of immunoglobulin on the expression of complement-activating molecules on the myocyte. For example, the expression of CD59 prevents formation of the effector molecule of complement (MAC, or the membrane attack complex, which binds to the target cell forming membrane pores).

**Is the Principle of Immunomodulation in CHF Wrong?**

There has been a great deal of research focused on understanding the role of the immune system in CHF. This has led several research groups to attempt clinical trials in patients with CHF using immunomodulatory therapy that have yielded less than encouraging results. However, the poor outcomes described in these studies may simply reflect our lack of understanding of immune processes in CHF. The frequently published observations demonstrating systemic changes (i.e., elevated type I cytokines) in patients with CHF have also been reported in many other pathological conditions and do not necessarily represent the immunologic events that occur at a localized site. In particular, elevated serum TNF-alpha does not exclusively represent systemic immune activation, or a systemic "skew" toward a Th1 response. Elevated TNF-alpha may be the result of a localized secretion at a sight of tissue damage/immune activation, which then enters the circulation and becomes detectable in blood. The observed increase in CD4+ T cells in patients with CHF [4] could represent cellular activation/motility in response to stress signals (including cytokines) in peripheral blood (CD4+ T cells...
may represent bystander cells in CHF). Clearly, a great deal of immune characterization is still required to understand the role and effect of immune activation in CHF. Another much ignored, yet potentially viable research avenue is in understanding how the myocardium alerts the immune system following the initial insult that might lead to the progressive syndrome of CHF. Indeed, CHF is a common pathway derived from a host of varying etiologies (e.g., myocardial ischemia and infarction, hypertension, viral infection, pregnancy, myocarditis), yet the symptomatic, histologic, and immunologic characterization of CHF, irrelevant of its cause, appears to be similar. Therefore, it is possible that myocardial damage acts as the “adjuvant” to immune activation via endogenous signals. This is a key area of research that the literature appears to be lacking.

**CHF and Endogenous Stress: Is the Myocardium in Control?**

Following an initial insult to the myocardium, for example, a coronary plaque rupture with resulting ischemic damage, cardiac workload is increased as myocytes enter a state of “hyperfunctionality.” Different cellular signaling pathways become activated, augmenting gene transcription and protein synthesis, which induces myocyte hypertrophy. If this process occurs for a sustained period, cardiac dilation and dysfunctional contractile motion occur, eventually leading to cardiac failure. This chronic process is the result of induced myocyte dysfunction, degeneration, and cell death.

Myocardial damage therefore initiates an immune response via the presentation of stress proteins (irrelevant to the cause of damage, including autoimmune processes that lead to myocarditis) (Fig. 1). Recent evidence has demonstrated that myocytes from failing rat hearts have increased expression of the endogenous stress protein, heat shock protein (HSP)60 (36). This increased expression was reported to occur as a result of mitochondrial damage or breakdown, a process that results in loss of contractile function and cell death. Heat shock protein 60 has also been implicated in CHF in humans (37). In this study, HSP60 expression was doubled in myocytes from patients with CHF compared with controls, yet the protective endogenous signal, HSP72, remained the same. The expression of HSP60 was localized within the myocyte plasma membrane on the cell surface, and it was also increased in blood plasma. This increase correlated with increased myocyte death. HSP60 is involved in peptide movement and mitochondrial function, but it also represents a ligand for activating receptors present on immune cells (toll-like receptors [TLRs]). Therefore, the evolutionary requirement for HSP60 to transfer from the mitochondria to the cell membrane suggests this protein acts as an endogenous immune danger signal. Interestingly, an activating receptor (TLR4) that binds to HSP60 is up-regulated by human myocytes from patients with heart failure (38). Theoretically, this allows the myocyte to “self-signal”; however, the signaling cascade that occurs following TLR4-HSP60 ligation in the myocyte is unclear. In general, HSPs represent a “danger signal” for in situ DCs (39). Following HSP recognition, DCs activate and migrate to lymph nodes where they stimulate adaptive immune responses. Interestingly, mitochondrial HSPs may have a protective effect against reactive oxygen species, which induce oxidative stress to the myocardium, a process that has been well reported in CHF (reviewed in Grieve and Shah [40]). The mitochondria is known to progressively and chronically produce reactive oxygen species (including superoxide and hydrogen peroxide) in the failing heart (41). This causes the modulation of calcium-dependent intracellular signaling cascades that are required for myocardial contraction (42) and results in myocyte dysfunction and death. However, recent evidence suggests overexpression of mitochondrial HSPs (including HSP10, HSP60, and HSP70) are associated with cellular survival and prevention of apoptosis (43,44), suggesting that HSP up-regulation in the mitochondria might be a survival mechanism, rather than an endogenous immune signal (these studies are limited to ischemia reperfusion animal models).

The up-regulation of HSP by the myocardium is therefore important, but not limited to reactions at the plasma membrane. Heat shock proteins are also secreted by damaged or necrotic cells (45), where they can mediate potent effects on the immune system. For example, HSPs (including HSP60 and HSP90) can act as peptide carriers/transporters and activate CD8+ T cells via cross-presentation of antigens (to major histocompatibility complex class I molecules) (46). Heat shock proteins activate CD4+ T cells and can induce the commitment of naïve (CD45RA+CD45RO−) T cells (47). Extracellular HSPs can also induce cytokine secretion, including TNF-alpha from APC via ligation with CD14 and TLRs (48). Extracellular HSPs have previously been associated with a range of conditions including atherosclerosis and vascular disease and are known to be secreted by damaged smooth muscle cells in vitro. This is clearly an area of importance in the heart failure setting.

The myocardium can induce positive leukocyte chemotaxis via the secretion of chemokines (where leukocytes migrate to the heart in response to increasing concentrations of chemokines) and also via the expression of chemokine receptors (49,50). For example, the chemokine CCL2 is elevated in explanted hearts from patients with CHF (49). This chemokine binds to its corresponding receptor, CCR2, on a range of cells including monocytes. Following endocardium CCL2:monocyte CCR2 ligation, monocyte activation occurs, leading to the production of cytotoxic compounds and reactive oxygen species. This causes endothelial damage and increased danger signal expression. Furthermore, endothelial gap junctions become damaged, allowing the infiltration of leukocytes into the myocardium, where further CCR2:CCL2 ligation has been associated with increased myocyte death (51).
The failing myocardium also provides signals to assist in leukocyte infiltration, via the up-regulation and/or secretion of cell adhesion molecules (CAMs). For example, the endothelium located in the microvasculature of human failing hearts increases the expression of several CAMs, including P-selectin, e-selectin, intracellular cell adhesion molecule-1, and vascular cell adhesion molecule-1 (52,53). This endothelial modification allows the transendothelial migration of a host of immune cells into the myocardium, including B cells, T cells, natural killer cells, monocytes, platelets, and DCs. Many of these CAMs are also known to elevate in a soluble form in the circulation from patients with CHF (54,55). This phenomenon has been described as representative of vascular inflammation. However, other evidence has demonstrated that soluble CAMs alter the functional capacity of circulating cells, suggesting the process represents specific signaling propagated by myocardial damage (56). In this study, peripheral blood mononuclear cells from patients with CHF adhered rapidly to human aortic endothelial cells (compared with peripheral blood mononuclear cells from healthy controls), a process that was associated with circulating CAMs. The investigators re-
ported that the adhesive capacity of peripheral blood mononuclear cells directly correlated with the concentration of circulating CAMs in the patient. This suggests that the failing myocardium secretes CAMs, which act as systemic activation signals for circulating cells.

The myocardium further controls its “fate” in response to stress, via alterations to the death receptor, Fas, following cell-cell contact with a Fas (ligand) L+ cell. Fas is a membrane-bound receptor involved in cell homeostasis. Under different conditions, Fas binding with FasL induces cell death. Resting myocytes constitutively express Fas, but following binding in normal conditions, cell death does not occur. However, myocytes exposed to ischemic conditions reorganize the downstream signaling events following myocyte Fas:immune cell FasL binding, so that myocyte death occurs (57).

Summary

Potentially the myocardium, rather than the immune system, exerts control over myocyte clearance (via cell death and removal). This concept is in keeping with the danger model of immunity. The danger model, first postulated by Matzinger (31) states that immune activation occurs in response to damage (or substances that cause damage), rather than substances that are foreign. The concept originally applied to pathogenic infections and neoplasia, but suitably “fits” with our current understanding of disease progression and immune involvement in CHF. The multifactorial etiologies that cause CHF via myocyte damage lead to a syndrome with identical disease characteristics. This could occur in whole or in part due to loss of self-tolerance and the recognition of auto-antigen, via presentation of endogenous ligands by the damaged myocardium.

Conclusions

Evidence suggests that the immune response in heart failure is a secondary phenomenon in response to myocyte injury. If this proves to be the case, successful treatment of CHF may be achieved by suppressing stress signals and thus restoring self-tolerance to the damaged myocyte. Ultimately, this approach might prove advantageous in comparison to the recent attempts of mere suppression of the immune system.

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