Inflammation in Heart Failure

The Holy Grail?

Jawahar L. Mehta, Naga Venkata K. Pothineni

Immuno-inflammatory mechanisms have been implicated in the initiation and progression of heart failure (HF) during the past 2 decades. Despite several investigators having postulated a pathogenic role of inflammation in HF, clinical trials of anti-inflammatory and anti-immune therapies in HF have not resulted in salutary effects. Absence of a beneficial effect of these therapies has led to more questions than answers. Is the presence of inflammation really bad? Is inflammation good at 1 time point and detrimental at another? Are there subsets of inflammatory cells that have a protective role and others that are detrimental? Extensive research to answer these questions has led to the identification of unique subsets of the immune cascade that might have a selective protective role in HF. One such group of cells is the CD4+ regulatory T cells (Tregs). These cells are a part of the adaptive immune response of the body and are further divided into natural and adaptive Tregs (Figure). Natural Tregs develop in response to an antigenic stimulation. Adaptive Tregs express a specific transcription factor called FoxP3 and are often termed as CD4+CD25+Foxp3+T cells. Tregs have been shown to have atheroprotective properties. Dinh et al showed that selective expansion of Tregs by cytokine-based interleukin-2 (IL-2)/anti–IL-2 monoclonal antibody complex therapy can attenuate atherosclerosis in mice.

Chronic HF is often associated with increased pulmonary pressures, defined as class II pulmonary hypertension. This increase in pulmonary pressures from left ventricular (LV) dysfunction is postulated to be the harbinger of right ventricular failure. In a previous study reported in 2012, Chen et al showed that LV pressure overload induced by chronic transverse aortic constriction in mice led to increase in right ventricular pressure and mass, along with an exponential increase in leukocyte and cytokine infiltration in the lung. Increased pulmonary pressures were associated with an increase in the expression of intercellular adhesion molecule-1, vascular cell adhesion molecule-1, ILs, tumor necrosis factor-α, and transforming growth factor-β, eventually leading to lung fibrosis.

In the current issue of Hypertension, this group of investigators report the results of proliferation of Tregs using the strategy used previously by Dinh et al in a pressure overload model of HF. Transverse aortic constriction for 4 weeks led to a significant drop in LV ejection fraction in the mice from 77% to 34% along with a 12-fold increase in LV end-diastolic pressure, doubling of lung mass and increased leukocyte infiltration in the myocardium and lung. To examine the effect of Tregs upregulation, intraperitoneal injection of IL-2/anti–IL-2 monoclonal antibody (IL-2/JES6-1) was performed on 3 consecutive daily doses every 6 days during the study period, once the LV ejection fraction reached ≥55%. Injection of IL-2/JES6-1 led to a 6-fold increase in Tregs in the spleen. Mice with LV dysfunction treated with IL-2/JES6-1 had significantly less reduction in ejection fraction, less increase in LV dimension, and lower rise in end-diastolic pressure. In addition, right ventricular weight and lung weight were significantly lower in the treated mice. Levels of various inflammatory markers such as IL-1β, tumor necrosis factor-α, and monocyte chemoattractant protein-1 were significantly elevated, whereas IL-10 expression was downregulated, in the lungs of mice with HF. Treatment with IL-2/JES6-1 led to a 5-fold increase in Tregs in the lungs of mice with HF, a decrease in proinflammatory cytokine expression and increased IL-10 expression. Treatment with IL-2/JES6-1 also led to a reduction in macrophages and T lymphocytes in the lungs. The investigators also demonstrated that IL-2/JES6-1 led to a reduction in transverse aortic constriction–induced increases of atrial natriuretic and β-myosin heavy chain protein content, along with a reduction in myocardial cytokine and lymphocyte infiltration. On the basis of these observations, the authors conclude that cytokine-induced upregulation of Tregs could have a protective role in preventing progression of a pressure overload model of HF and also inhibit pulmonary remodeling and fibrosis.

The findings of this study provide a succinct bidirectional link between inflammation and HF progression, and we commend the authors for a study well done. These results, however, raise some important questions. What is the precise role of inflammation in HF? Does the increase in inflammatory markers represent the primary pathogenic pathway that determines clinical outcomes or the final common pathway of many other signaling mechanisms? Negative results seen in a multitude of anti-inflammatory trials in HF makes one wonder if the appropriate signaling mechanisms are being targeted. A second area of uncertainty is the role of lung inflammation in the progression of HF and its effect on HF progression and treatment.
of HF. Increased inflammatory markers in the lung in HF could just represent a nonspecific response induced by chronic pressure overload in the LV, rather than a primary pathogenic pathway of lung injury. In fact, lung inflammation could just represent 1 component of a systemic inflammatory response in HF. Increased inflammatory signaling has been reported in end organs such as the kidney, brain, and liver in patients with HF. Lu et al observed severe renal dysfunction and fibrosis in mice subjected to chronic coronary artery ligation. This was associated with increase in renal IL-1β, vascular cell adhesion molecule-1, and thiobarbituric acid reactive substances, and structural alterations in the kidney as well a marked increase in circulating proinflammatory cytokines. These authors did not examine the pulmonary tissues, but it would not be surprising if the lungs revealed a marked inflammatory response after prolonged HF state akin to the observation of Wang et al. Are these changes in the lungs, kidneys, and other organs in chronic HF manifestations of a systemic process? Almost all protective and regenerative inflammatory mechanisms in the body use common signaling mediators. For example, transforming growth factor-β is a common mediator inducing fibrosis in almost every organ. How can the increased expression of this nonspecific marker in the lung be the primary pathogenic event leading to pulmonary fibrosis and reactive hypertension in HF? It is more plausible that it is just represents a common final mechanism. A third important question that remains unanswered is if all HF is created equal, can the pathogenic responses of inflammation in a pressure overload model of HF be extrapolated to an ischemic model? If the answer is yes, why are there striking differences in the presentation, management, and outcome of these conditions? Presence of similar degrees of inflammation would certainly not explain these clinical differences, making the case for inflammation being a final common pathway rather than a primary trigger. Finally, based on evidence available thus far, immune modulation by cytokine guided therapy seems to have promise in halting the progression of atherosclerosis and HF. Whether this could materialize into clinical benefit remains an unanswered question. The study by Wang et al is a relevant extension of the work by Dinh et al on the contribution of inflammation in HF. The data presented provide fuel to further investigate and understand this exciting, vastly explored, yet undeciphered field of immunomodulation in not just HF but also in cardiovascular diseases where inflammation has been thought of as a pathogenic villain.

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References


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