TNF-α and Heart Failure
The Difference Between Proof of Principle and Hypothesis Testing

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Cachexia (from the Greek kakos, meaning bad, and hexis, a state of being) has both fascinated and challenged clinicians and scientists for many years. It has been known since the earliest descriptions of heart failure that cachexia can be associated with the late stages of the syndrome. Cachectin, a hormone that suppresses the expression of lipoprotein lipase and other anabolic enzymes in fat, was purified in 1985.1 Tumor necrosis factor (TNF) had been isolated much earlier, in the 1970s.2 After the purification of cachectin, the complementary DNAs and genes encoding each protein were cloned almost immediately and were shown to be identical.3 Cachectin and TNF were one and the same. Since then, considerable evidence has accumulated suggesting a role of TNF in various inflammatory conditions,4 and TNF-α is now known to be one of the most pleiotropic of all cytokines. Among a large number of cellular responses to TNF-α, it is immuno-regulation, transcriptional regulation, cytotoxicity, and antiviral activity.5 Two distinct TNF-α receptors occur on multiple cell surfaces: a 55-kDa (TNF-R1) and a 75-kDa (TNF-R2) protein, with the TNF-R1 receptor subserving most of the activity of TNF, including cytotoxicity, fibroblast proliferation, bacterial resistance, prostaglandin E₂ synthesis, antiviral activity, and induction of superoxide dismutase.6 The TNF-R2 receptor subserves T-cell proliferation, dermal necrosis, and insulin resistance, although there are overlapping activities between TNF-R1 and TNF-R2. The cytoplasmic domains of the 2 receptors are structurally different, suggesting distinctive evolutionary signal transduction pathways.

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Trimeric TNF-α binds to several cell-surface receptors simultaneously, crosslinking the receptors to initiate signal transduction. There is the possibility that shedding of surface membrane TNF-α receptors in patients with heart failure and increased circulating levels of TNF-α may combine to neutralize the biological actions of TNF-α in heart failure.6 Soluble circulating TNF-α receptors may bind to circulating TNF-α, rendering the cytokine less active. Alternatively, a protein can be genetically engineered that couples, or fuses, the Fc portion of heavy-chain IgG to the extracellular domain of the TNF-α receptor, rendering the TNF-α molecule less active. Chimeric inhibitors of TNF-α are now beginning to emerge as potential new anti-inflammatory drugs, and it is natural that they be considered for heart failure.

It has been nearly a decade since Levine et al.,7 using a bioassay system, provided evidence demonstrating that circulating levels of TNF-α are elevated in patients with severe chronic heart failure. Because of repeated observations that TNF-α is increased in the blood of patients with cardiac injury, including inflammatory myocarditis,8,9 acute myocardial infarction,10 and unstable angina pectoris,11 it is reasonable to assume that it evolved as one of many protective responses to cellular injury. Over the past decade, Mann and his group have performed a series of experiments examining the role of TNF-α in both experimental and clinical heart failure. Among the findings are data demonstrating that TNF-α production is induced in cardiac myocytes12 and that chronic infusion of TNF-α in rats produces left ventricular contractile dysfunction and dilatation.13 Supporting evidence that overproduction of TNF-α by cardiac myocytes is sufficient to cause severe cardiac disease has been provided by Bryant and colleagues,14 who overexpressed the protein in hearts of transgenic mice, leading to a phenotype characterized by systolic dysfunction, cardiac inflammation, ventricular dilatation, congested tissue, and increased mortality. Another transgenic line of mice from Feldman’s laboratory also overexpressed TNF-α, albeit at a lower level, producing a phenotype with dilated cardiomyopathy without much inflammation.15 The Feldman experiments used a single transgenic line, and the gene dose effect is not clear. Yet, the accumulated evidence supports the concept that this cytokine, like the neurotransmitter norepinephrine and the peptides angiotensin II and endothelin, helps to orchestrate a response to injury that ultimately leads to cardiac dysfunction and progressive heart failure. There is now proof of principle for this important concept. In the aggregate, these findings also support the broader hypothesis that neurohumoral activation and cytokine production contribute importantly to the pathogenesis of progressive heart failure.

An experiment of nature further supports the possible role of TNF-α in the genesis of progressive heart failure. The recently described mutation of a gene that normally encodes for AMP deaminase 1 (AMPD1) may be associated with delayed progression of heart failure.16 As a consequence of diminished adenosine deamination, patients having a mutation in the AMPD1 gene may develop heightened intracellular cardiac myocyte adenosine levels. High levels of cardiac myocyte adenosine would then be expected to attenuate TNF-α expression,17 thus retarding progression of heart failure and providing a potential mechanism whereby a point mutation may benefit patients.

In the case of the sympathetic nervous system and the renin-angiotensin-aldosterone system, the neurohumoral hypothesis has

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been tested beyond proof of principle. There is now abundant clinical evidence that ACE inhibitors and β-adrenergic blocking agents favorably alter the natural history of patients with heart failure. Recently published guidelines recommend the use of ACE inhibitors and β-adrenergic blockers for the treatment of chronic heart failure, although additional data regarding the use of β-adrenergic blockers in patients with NYHA classes I and IV are eagerly awaited. In the case of TNF, we also have proof of principle, but hypothesis testing remains incomplete.

In the current issue of *Circulation*, Deswal et al report on the use of a soluble p75 TNF receptor fusion protein that essentially blocks the effects of TNF in a small group of patients with NYHA class III heart failure and elevated TNF-α levels. Patients were randomly allocated to treatment or vehicle in a double-blind dose-escalation study to examine the safety and potential efficacy of a single intravenous infusion of etanercept, a TNF fusion protein antagonist. The results indicate no significant side effects, a decrease in the biologically active levels of TNF-α, and an increase in quality-of-life scores, 6-minute walk distance, and ejection fraction. The study offers further proof of principle and suggests a green light to proceed with a large-scale clinical trial to further test the cytokine hypothesis. Such a trial is about to be launched with the p75 TNF receptor fusion protein in patients with heart failure.

As with all preliminary phase I and II trials, caveats are in order. The numbers of patients receiving the full dose are very small. Absolute values for the end points are not provided; rather, the authors elected to provide only percent change from baseline and did not make comparisons against placebo. The dose of etanercept that will prove both safe and most effective must be carefully determined. Recent data suggest that 12 mg/m², slightly higher than the maximum dose of 10 mg/m² used by Deswal et al, may be more effective. The time course over which the fusion protein must be given is not clear. Why did the investigators choose to block the TNF-R2, when the preponderance of TNF biological activity, including apoptosis, is mediated by TNF-R1? Is there a rebound hemodynamic deterioration if the fusion protein dose is reduced or stopped? As with all immuno-modulators, will such patients be at risk for infection? Unlike rheumatoid arthritis and inflammatory bowel disease, for which TNF inhibitors show great promise, heart failure is not generally considered to be a purely inflammatory condition. It is a highly complex syndrome that incorporates many noninflammatory features, such as growth, apoptosis, heightened matrix metalloproteinase activity, protein isoform switches, altered Ca²⁺ transients, and unusual mechanical forces on integrins that signal the nucleus through a variety of pathways. The quantitative contribution that cytokines make toward the pathophysiology of heart failure is still not clear. Despite these caveats, the Mann laboratory is to be congratulated for fulfilling Koch’s postulates with a highly innovative treatment strategy. We have proof of principle. The cytokine hypothesis, however, remains to be tested, and only a large randomized clinical trial can provide this forum.

**References**

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