Starve a fever to heal a heart? Interleukin-18 gives new meaning to an old adage

Fadi G. Akar
The Cardiovascular Institute, Ichan School of Medicine at Mount Sinai, New York, New York

While inflammation is required for proper healing of the myocardium following injury, its unabated persistence promotes the development of pathological hypertrophy and accelerates the progression to decompensated heart failure (5, 10, 11). Inflammation is activated by the so-called inflammasome, a macromolecular complex that senses the initial injury and responds to it by releasing multiple cytokines and chemokines, including TNFα, interleukin (IL)-1β, IL-18, and others (11). While mechanisms by which TNFα and IL-1β alter myocyte function are well documented, those mediated by IL-18 are only beginning to be unveiled. In this issue of the American Journal of Physiology-Heart and Circulatory Physiology, Li et al. (8) bridge a major gap in our understanding of the role of IL-18 in the heart by highlighting de novo effects that are dependent on autophagy, a critical lysosomal degradation pathway activated by nutrient starvation.

IL-18 as a therapeutic target. As a member of the IL-1 family, IL-18 is implicated in the pathophysiology of prevalent cardiac diseases, including myocardial infarction and pressure overload hypertrophy. The utility of IL-18 as a biomarker for heart disease is underscored by the fact that elevated IL-18 plasma levels are associated with disease progression in patients with coronary artery disease and with increased mortality in patients with advanced heart failure (13). The active role of IL-18 in mediating adverse remodeling is supported by in vitro and in vivo studies. For one, treatment of human atrial myocytes (HL-1 cells) with IL-18 causes substantial hypertrophy because of activation of the phosphatidylinositol 3-kinase-Akt pathway. Similarly, chronic administration of IL-18 to mice results in the development of left ventricular hypertrophy along with fibrosis and impaired ventricular function. The role of IL-18 as a putative therapeutic target is inferred by its increased myocardial expression at both the mRNA and protein levels in the failing human heart (9, 10) and in multiple animal models of hypertrophy and heart failure (2, 12). Collectively, these studies emphasize the pathophysiological consequences of increased myocardial IL-18 levels and suggest the potential for pharmacological or gene-based approaches to inhibit the function or restore the expression of this maladaptive cytokine in an attempt to improve myocardial function. To that end, strategies involving the use of IL-18 neutralizing antibodies or an IL-18 binding protein have been proposed (10). Both approaches, which achieve IL-18 inhibition (4), are undergoing clinical testing for psoriasis, rheumatoid arthritis, and type 2 diabetes mellitus. But will these approaches be effective and safe in combatting heart disease?

To address this important question, basic studies are urgently needed to define the exact biological role of IL-18 in the heart. Clearly, genetic mouse models with IL-18 ablation (IL-18 knockout mice) can shed important light on this issue. To date, however, studies using IL-18 knockout mice have yielded discrepant results that are fueling a debate regarding the therapeutic potential of IL-18 inhibition. Whereas one study clearly documents protection of IL-18 knockout mice against IL-1β-induced left ventricular dysfunction (12), other studies are showing either neutral or deleterious effects (2, 3, 14). For example, genetic ablation of IL-18 failed to protect mice against hypoxia-induced right ventricular hypertrophy possibly because of compensatory upregulation of other inflammatory cytokines and chemokines in response to the prohypertrophic stimulus (2). Moreover, abrogation of the compensatory phase of hypertrophy following transaortic constriction worsened the outcome of IL-18 knockout mice as these animals underwent accelerated disease progression compared with their wild-type counterparts (3). Despite the growing evidence that IL-18 ablation can impart a detrimental effect on the myocardial response to stress, mechanisms underlying this seemingly paradoxical observation remain largely unknown, at least until now.

In their article, Li et al. (8) provide a provocative explanation for why germline elimination of a disease-causing cytokine is deleterious. Through a systematic approach involving ultrastructural, histological, biochemical, and functional measurements, these authors elegantly demonstrate an intriguing inflammation-independent effect of IL-18 deletion on basal myocardial function. They report clear evidence of cardiac hypertrophy and impaired exercise tolerance of IL-18 knockout mice. Underlying this hemodynamic deficit are ultrastructural and functional abnormalities in mitochondria as well as altered phosphorylation and localization of the main ventricular gap junction protein, Cx43. These molecular changes are indicative of impaired metabolism and cell-to-cell communication, respectively. Indeed, the elegant study by Li et al. (8) puts forth a unifying hypothesis to explain the metaboloelectrical abnormalities that arise as a consequence of IL-18 deficiency.

Too much or too little: the double-edge sword of IL-18. As with any good study, the article by Li et al. (8) leaves us with burning questions regarding the physiological role of this proinflammatory cytokine. For one, the study highlights the relevance of IL-18 in the maintenance of proper Cx43 localization and phosphorylation. We and others previously documented the importance of Cx43 dephosphorylation and lateralization in the pathogenesis of conduction-dependent arrhythmias in small and large animal models of hypertrophy and heart failure (1, 7). We also implicated autophagosomes in the displacement of the lateralized pool of Cx43 (6). In light of these studies, it will be important to investigate whether the ultrastructural and biochemical changes in Cx43 that are mediated by IL-18 gene deletion are sufficient to cause functional changes in gap junction conductance and impaired cell-to-cell coupling. Broadly speaking, studies are needed to define the
cellular and tissue-level electrophysiological changes associated with IL-18 dysregulation to avoid potential proarrhythmic activity when targeting this proinflammatory pathway.

Another major question relates to the relevance of findings from IL-18 knockout mice to real-world therapeutic applications. A clear limitation inherent in the use of transgenic mouse models is the strong potential for significant gene reprogramming during development. Therefore, a more powerful experimental approach to address the role of IL-18 in the adult heart entails the generation of cardiac-specific conditional IL-18-deficient mice in which the cytokine is silenced at the time of injury to simulate the clinical scenario.

Since a basal level of IL-18 seems to be essential for the maintenance of normal cardiac function, efforts to determine the dose-dependent effects of IL-18 inhibition are urgently needed. Such studies will ultimately reveal the possibility of maximizing the benefits of targeted IL-18 therapies by titrating the levels of this cytokine within an optimal range that suppresses pathological remodeling without inhibiting autophagic processes. Of note, gene approaches to overexpress and silence IL-18 in a dose-dependent manner would be a powerful complement to the transgenic mouse models. Nonetheless, the present study reaffirms the importance of recognizing the rich biological diversity and redundancy in cytokine signaling when considering long-term inhibition of a given member of the IL family. Indeed, comprehensive analysis of inflammatory pathways is warranted when a prominent cytokine, such as IL-18, is manipulated.

When we consider the established principle that IL-18 overexpression promotes pathological hypertrophy, a major unexpected finding of this report is the presence of significant cardiac hypertrophy at baseline in IL-18 knockout mice. This reasserts the notion that too much or too little IL-18 is detrimental. Apparently, upregulation and downregulation of this cytokine result in the identical cardiac disorder by activating divergent mechanisms (inflammation and impaired autophagy, respectively). In summary, the elegant paper by Li et al. (8) ascribes a de novo role for a major proinflammatory cytokine in the heart. These original findings should spur new efforts to control the dosage, timing, and chronicity of IL-18 inhibition for combating heart disease.

REFERENCES


