Tumor Necrosis Factor and Viral Myocarditis
The Fine Line Between Innate and Inappropriate Immune Responses in the Heart

Douglas L. Mann, MD

“‘In this world there are only two tragedies. One is not getting what one wants, and the other is getting it.’”
—Oscar Wilde

Tumor necrosis factor (TNF) has been referred to as a “mixed blessing for higher organisms.”1 That is to say, although the controlled self-limited expression of TNF plays a critical role in activating host defense mechanisms and in homeostatic tissue repair, uncontrolled overexpression of TNF produces devastating consequences for the host organism, frequently leading to diffuse inflammation, multiorgan dysfunction, hemodynamic collapse, and death. Although a similar “bifunctional picture” for TNF has not yet emerged clearly for the heart, the report by Wada and colleagues2 in the present issue of Circulation suggests that TNF may be a mixed blessing for the heart as well.

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Several lines of evidence suggest that proinflammatory cytokines, such as TNF, play an important role in the pathogenesis of viral myocarditis. For example, elevated levels of TNF have been reported in patients with viral myocarditis.3 Importantly, TNF mRNA and protein are consistently upregulated in the hearts of patients with viral myocarditis.4 Mice with targeted overexpression of TNF in the cardiac compartment develop florid myocarditis and progressive myocardial fibrosis.5,6 The exogenous administration of TNF aggravates myocarditis, and the neutralization of TNF by antibodies or soluble receptors attenuates viral myocarditis.7,8 Taken together, these observations suggest that TNF plays an important pathophysiological role in the development and progression of viral myocarditis. In the present issue of Circulation, Wada and colleagues2 report that mice with targeted disruption of the TNF gene (TNF−/−) had increased mortality after infection with the encephalomyocarditis virus compared with wild-type mice (TNF+/+). Moreover, they showed that exogenous administration of TNF prevented the increase in virus–induced mortality in the TNF−/− mice. On the basis of the findings in their study, Wanda et al2 conclude that TNF is cytoprotective in the setting of acute viral myocarditis. How can we reconcile these 2 different sets of experimental observations, one of which clearly suggests that TNF is sufficient to produce deleterious effects and the other which suggests that TNF is necessary for survival? To address this question, it is first necessary to digress for a moment to discuss the concept of innate immunity in the heart.

Innate Immunity

The immune system evolved under selective pressure imposed by infectious microorganisms. As a result, all multicellular organisms have developed various defense mechanisms that have the capacity to protect the host organism by destroying invading microorganisms. The immune system has traditionally been divided into innate and adaptive components, each of which has a different role and function in defending the host organism against infectious agents.9 The innate immune response is a preprogrammed (ie, germ-line-encoded), nonspecific first-line of defense that is primarily responsible for eliminating and/or containing microorganisms at the site of entrance into the host. To impede the entrance of infectious microorganisms, the innate immune system has developed a series of phylogenetically conserved receptors, termed pattern-recognition receptors, that have the ability to recognize specific pathogen-associated molecular patterns that are characteristic of certain families of infectious agents. For example, the lipopolysaccharides of Gram-negative organisms, the teichoic acids of Gram-positive organisms, the glycolipids of mycobacterium, the mannans of yeast, and the double-stranded RNAs of viruses are representative examples of pathogen-associated molecular patterns that are unique to these pathogens and, in some cases, that are required for their virulence. Importantly, these pathogen-associated molecular patterns are not expressed by the host organism. Thus, one of the quintessential features of the innate immune system is that it allows the host to accurately and rapidly discriminate self from non-self. In contrast, the adaptive immune system takes 3 to 5 days to develop fully, and it is organized around 2 classes of specialized cells, T cells and B cells. These lymphocytic cells display a single kind of structurally unique receptor that arises as a result of random genetic mechanisms. As a result of these genetic variations, the receptors on these lymphocytic cells can react with an extremely broad variety of different infectious microorganisms. Once the receptor is engaged on lymphocytic cells, the foreign antigen triggers the activation and proliferation of these cells. This process, called clonal selection, accounts for most of the basic properties of

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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(Circulation. 2001;103:626-629.)

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Circulation is available at http://www.circulationaha.org
the adaptive immune system and is absolutely necessary for the generation of an efficient long-term immune response.

Innate immune recognition is mediated by a structurally diverse set of pattern-recognition receptors that belong to several different protein families. Functionally, the pattern-recognition receptors can be divided into the following 3 groups: humoral proteins circulating in the plasma (e.g., CD14, the endotoxin receptor, and complement), endocytic receptors expressed on the cell surface, and signaling receptors that are expressed on the surface of the cell (e.g., toll receptors). The distribution of these cellular pattern-recognition receptors occurs both on the cells that are likely to encounter infectious agents and on cells that are capable of activating the adaptive immune response. Once the pathogen-associated molecular pattern is recognized by its cognate pattern-recognition receptor, these receptors will trigger the expression of a programmed series of endogenous signals that are capable of eliciting a full inflammatory response (see below).

One of the more interesting examples of a pattern-recognition receptor is the recently described Toll/nuclear factor (NF)-κB host defense pathway that was first described in the fly Drosophila. A loss-of-function mutation in the toll gene resulted in increased susceptibility to fungal infections in Drosophila; however, it had no effect on the susceptibility of the fly to bacterial infections. Recently, homologues of the Drosophila toll, termed toll-like receptors (TLRs), have been identified in higher vertebrate species, including mammals. The first human toll characterized was TLR-4, which activates the NF-κB signaling pathway that is critical for upregulating the expression of a variety of inflammatory mediators. As shown in the Figure, the activation of TLR-4 by lipopolysaccharide (a classic pathogen-associated molecular pattern) induces the expression of proinflammatory cytokines (TNF, interleukin [IL]-1, interleukin-6, and interferon [IFN]-γ), cell adhesion molecules, and inflammatory cells (neutrophils, monocytes, and natural killer cells).

TLR-4 in mammalian heart: this receptor is capable of recognizing specific pathogen-associated molecular patterns (PAMPs) that are part of infecting microbes. In this example, recognition of lipopolysaccharide (LPS) on Gram-negative organisms occurs after binding of CD14 (endotoxin receptor) to lipopolysaccharide, which then leads to binding of this complex to TLR-4, a pattern-recognition receptor (PRR). As shown, another protein, termed MD-2, is also required for TLR-4 to bind to lipopolysaccharide. Once TLR-4 is activated, it is capable of triggering the activation of transcription factor NF-κB, which then triggers an inflammatory response that is composed of proinflammatory cytokines (TNF, interleukin [IL]-1, interleukin-6, and interferon [IFN]-γ), cell adhesion molecules, and inflammatory cells (neutrophils, monocytes, and natural killer cells).

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tional cytokines and costimulatory molecules by antigen-presenting cells that are required for the activation of the adaptive immune system.\textsuperscript{13} Is there an innate immune system in the heart? At the time of this writing, there are 2 distinct lines of evidence that suggest that the myocardium possesses a functionally intact innate immune system. First, there is substantial evidence now that the mediators and effectors of the innate immune response, including proinflammatory cytokines, nitric oxide, and chemokines, are expressed in the adult mammalian heart by cardiac myocytes in response to challenge with classical pathogen-associated molecular patterns, such as lipopolysaccharide and viral particles.\textsuperscript{4,13} Second, the heart expresses at least 2 pattern-recognition receptors for pathogen-associated molecular patterns. That is, studies have demonstrated that CD14, the soluble pattern-recognition receptor for lipopolysaccharide, is expressed by adult cardiac myocytes.\textsuperscript{14} Moreover, TLR-4 mRNA and protein were recently described in adult cardiac myocytes and microvascular endothelial cells from the heart.\textsuperscript{15} Finally, very recent observations suggest that TLR-4 is critical for lipopolysaccharide-mediated activation of proinflammatory cytokine expression in the adult mammalian heart (Jesus Vallejo, MD, personal communication of proinflammatory cytokine expression in the adult cardiac myocytes). Thus, taken together, these observations provide presumptive evidence for a functionally intact innate immune system in the heart.

Conclusions

Viewed within the context of the above discussion, the results of the findings by Wada and colleagues\textsuperscript{2} in the present issue of Circulation suggest that a loss of TNF signaling in the TNF\textsuperscript{−/−} mice led to a disruption of the innate immune response in the heart. That is, the absence of TNF signaling prevented the upregulation of cellular adhesion molecules, which in turn prevented the recruitment of neutrophils, monocytes, and natural killer cells to the areas of the myocardium where the encephalomyocarditis virus had infected the myocytes. This allowed the virus to multiply unchecked, thereby increasing its cytopathogenic effects in the cardiac myocytes, which ultimately led to increased mortality. What is not clear from the present study and will thus require further investigation is whether the increased mortality in the TNF\textsuperscript{−/−} mice was also related to the inability of the innate immune system to activate the adaptive immune system.

If TNF expression in the heart is part of an evolutionarily conserved innate immune system and if the fundamental role of the innate immune system is to rid the host of infectious agents without damaging “self,” why then is TNF expression within the heart often associated with maladaptive inflammatory reactions that lead to increased tissue damage and, in some cases, to increased mortality? Unfortunately, the answer to this 600-million-year-old conundrum is not known. One potential explanation, albeit speculative, is that the phylogenetically ancient innate immune system was selected for the purpose of providing a rapid and effective immune response in organisms that reproduced early and had relatively short life spans (ie, weeks to months). Thus, from a evolutionary perspective, it is possible that nature may have conserved molecules that conferred short-term benefits in the host but that also had the potential for long-term detrimental effects. The long-term detrimental effects escaped early evolutionary selection pressures because they did not present a problem for hosts with short life spans. Presumably then, as the innate system became integrated with the more sophisticated adaptive vertebrate immune system, the short-term benefits conferred by the innate immune system continued to outweigh the long-term detrimental effects of this system.

This point of view is consistent with our current clinical understanding of viral myocarditis in humans, in which most (but certainly not all) examples of immune-mediated injury in the heart are self-limited and do not, for the most, part lead to catastrophic myocardial damage. Indeed, the left ventricular dysfunction that develops after viral myocarditis is usually modest and is, in general, partially reversible. Moreover, the symptomatic heart failure that supervenes after viral myocarditis may not develop for a period of 3 to 5 years. Thus, it would seem that the activation of the innate immune system may be a mixed blessing for the adult mammalian heart. Nonetheless, the important question that arises from the foregoing discussion, as well as from the work presented by Wada et al,\textsuperscript{2} is whether it will be possible to modulate the inappropriate/maladaptive consequences of innate immune activation and proinflammatory cytokine expression in the mammalian heart while preserving the important advantages that this phylogenetically conserved immune system provides to the host. Given how little we know about innate immune responses in the heart at present and given that there are probably hundreds of different pattern-recognition receptors in the heart that have yet to be characterized, it is almost certain that our learning curve will be extremely steep for the foreseeable future.

Acknowledgments

The author thanks Mary Helen Soliz for secretarial assistance, Dr Ralph A. Kelly for first introducing him to the concept of innate immunity, and Erica L. Mann for her inestimable help with “word-smithing” the title.

References


**Key Words:** Editorials • tumor necrosis factor • myocarditis • cytokines • inflammation
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Circulation. 2001;103:626-629
doi: 10.1161/01.CIR.103.5.626

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