This Review is in a thematic series on Myocardial Inflammation, which includes the following articles:

The Fire Within: Cardiac Inflammatory Signaling in Health and Disease

Inflammation in Myocardial Disease
Autoantibodies in Heart Failure and Cardiac Dysfunction
Regulation of the Inflammatory Response in Cardiac Repair
Inflammation, Endoplasmic Reticulum Stress, Autophagy, and the Monocyte Chemoattractant Protein-1/CCR2 Pathway
Signaling Pathways in Response to Inflammation, Senescence, and Aging in the Heart

Anthony Rosenzweig, Guest Editor

The Fire Within: Cardiac Inflammatory Signaling in Health and Disease

Matthew Coggins, Anthony Rosenzweig

Abstract: Inflammatory mediators are operative in the pathogenesis of the most common forms of heart disease. Although in most cases the induction of these pathways is maladaptive and deleterious, there are notable exceptions when inflammatory pathways participate in healing or limiting the extent of injury. The appreciation of the role of these mechanisms in myocardial homeostasis and pathophysiology has led to increased efforts to elucidate the specific signaling pathways most relevant to the heart. Our goal in this introductory overview is to provide context for the five detailed reviews that follow by introducing the major relevant stimuli, the receptors, and pathways that mediate inflammatory signaling in the heart. We try to impart a sense of the scope and complexity of these pathways, as well as their interactions with signaling pathways regulating cell survival and metabolism. These complexities underscore the potential challenges of therapeutically targeting inflammatory mechanisms in heart disease and may help explain the mostly disappointing results of this approach to date. (Circ Res. 2012;110:116-125.)

Key Words: heart failure ■ ischemia ■ myocardial inflammation ■ signal transduction

The term “inflammation” comes from the Latin word inflammare, meaning to set on fire, an acknowledgment of one of the four cardinal signs of inflammation first recognized by Celsus almost 2000 years ago and memorized by many generations of medical students since. Galen felt the initial inflammatory response could have protective effects but might ultimately become adverse, requiring bloodletting. In the 19th century, Virchow emphasized the adverse effects of inflammation and introduced functio laesa, or loss of function, as a fifth cardinal sign.

Much has changed since these early observations, yet important themes persist. We now recognize inflammation as a set of inter-related processes and intersecting mechanistic pathways, rather than solely a constellation of signs and symptoms. In recent years, research has unraveled a remarkable and complex series of molecular mechanisms constituting the inflammatory response. This new molecular understanding provides important tools to study the role of these pathways in cardiovascular health and disease, as well as new insights into the dual nature of inflammation and how it leads to loss of function.

The current series focuses on the molecular mechanisms and functional effects of inflammation in the heart, where these themes are also evident. In the heart, inflammation-
driven loss of function remains a major clinical problem. This series details recently elucidated mechanisms contributing to this dysfunction. In addition, although cardiac inflammation is generally seen as maladaptive, we also see that these pathways may participate in healing and repair. In some instances, the duality of beneficial and deleterious effects is evident, even within the same pathway, which might drive potentially harmful inflammation as well as promoting cardiomyocyte survival, as in the case of nuclear factor kappa B (NF-κB). In other cases, this duality is manifest in newly identified molecular pathways that participate in healing or actually turn off potentially harmful inflammatory cascades. The Table offers a simplified outline of the duality in the pathways discussed here, providing examples from many studies that have demonstrated contrary outcomes from experimental manipulation of the pathways in the heart. These complexities and the double-edge nature of the molecular pathways involved complicate approaches to therapeutic targeting of inflammatory signaling.

The current series includes five reviews. Bruce McManus et al review the specific pathways and mechanisms contributing to cardiac dysfunction in four classic settings marked by inflammation: ischemia-reperfusion injury, sepsis, myocarditis, and transplant rejection. Their review includes an interesting discussion of the role of the complement cascade in allograft rejection and ischemic injury. Nikolaos Frangogiannis describes recently identified endogenous inhibitors induced as part of the core inflammatory response that actually serve to suppress inflammation after infarction. Aging is a dominant risk factor for cardiovascular disease and other diseases associated with inflammation, including cancer and metabolic disease. John Papaconstantinou et al detail some of the potential links between aging and inflammatory signaling, with a particular focus on the roles of oxidative stress and the ASK1 signaling cascade. Pappachan Kolattukudy and Jianli Niu review the role of ER stress and inflammation, with an emphasis on newly discovered roles for the chemokine monocyte chemoattractant protein-1 (MCP-1) and its downstream effector and novel zinc finger protein, MCP-1-induced protein. Finally, Hugo Katus and colleagues examine the role of specific autophotodies in cardiac dysfunction and heart failure. Each of these contributions illustrates specific ways in which inflammatory signaling has an important impact on the heart and demonstrates the complexities and intersections of the relevant molecular mechanisms. To set the stage, we introduce key stimuli, pathways, and players (Figure).

Initiation of the Inflammatory Response in the Heart
Most inflammatory and immune responses have evolved to protect us against invading pathogens. Whereas this may have relevance in some cardiac conditions, in most settings the primary stimuli driving cardiac inflammation are incompletely understood. A broad range of biomechanical stimuli induce an inflammatory state in the myocardium. In addition to the relatively rare instances of inciting infectious agents, myocardial injury, hemodynamic stress, circulating cytokines, and autoimmune reactions all induce cardiac inflammation. Hemodynamic stress is often modeled in animals by transverse aortic constriction, which leads to an initial adaptive hypertrophic response, followed by dilative remodeling and development of systolic failure, characterized by fibrosis, apoptosis, and inflammation. Even in this model, the inflammatory triggers are not entirely certain. Myocardial strain induces interleukin (IL)-6 production, which leads to activation of JAK/STAT signaling. Mechanical strain in vascular wall (as well as the myocardium) likely also contributes through production of reactive oxygen species, MCP-1, and transforming growth factor-β1, which induce macrophage

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infiltration. Multiple strategies that interrupt or antagonize the inflammatory cascade appear to attenuate the heart failure phenotype. Inflammatory signaling in cardiomyocytes also may be initiated through canonical pathways involving extracellular cytokine stimulation of cell surface receptors. Cytokines may be released from neighboring cardiomyocytes as a result of inflammatory activation, thus amplifying the inflammatory signal to multiple cells. Cytokines also may be released from immune cells recruited to the myocardium. The common cytokines involved and relevant pathways are described. As reviewed by Katus et al, an adaptive immune response directed at specific antigens in the myocardium also can initiate myocardial inflammation. Finally, activation of signaling may proceed through dedicated cell surface receptors such as toll-like receptors (TLR), the primary routes of activation of innate immune signaling, in response to incompletely understood ligands. Some of the specific participants and mechanisms are outlined.

### Signaling Cascades

**TLRs**

These pathways recently have been reviewed in detail and thus we confine ourselves here to a few general comments. TLR pathways are typically activated in response to pathogen-associated molecular patterns (typical of infectious agents) or danger-associated molecular patterns (originating in tissue injury). The TLRs predominantly expressed in cardiomyocytes are TLR2, TLR3, and TLR4. The mRNA levels of ten TLRs have been defined in human heart tissue, although protein expression has not. TLR 4 expression is increased in cardiomyocytes of rodents and in heart tissue of

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CM indicates cardiomyocyte; EAM, experimental autoimmune myocarditis; LPS, lipopolysaccharide; LV, left ventricular; MI, myocardial infarction; NF-κB, nuclear factor kappa B; TAC, transverse aortic constriction; TLR, toll-like receptor; TNF, tumor necrosis factor.
patients with heart failure.\textsuperscript{16–18} TLR signaling has a capacity for both beneficial and deleterious effects on the myocardium. In a beneficial role, acute activation such as seen after transient ischemia or with serum deprivation in vitro leads to a cytoprotective effect and can actually enhance cardiomyocyte function.\textsuperscript{19–21} Beneficial effects can be mediated by TLR4–IRAK1 signaling\textsuperscript{19} and a TLR2–TIRAP pathway,\textsuperscript{14} among others. The effects of chronic TLR activation have been studied in mouse models of myocardial ischemia-reperfusion and infarction, utilizing mice with mutation or deletion of TLR4, TLR2, or MyD88.\textsuperscript{14} These studies overall show that TLR signaling contributes to worsened left ventricular dysfunction, larger infarct size, and recruitment of inflammatory cells. Notably, the specific endogenous ligands for TLR signaling in these conditions remain to be identified.

TLR signaling classically leads to activation of NF-κB, in addition to type I interferon production.

**Tumor Necrosis Factor and NF-κB**

The role of tumor necrosis factor (TNF)\textsuperscript{a} signaling and NF-κB activation in the heart also has been recently reviewed, and the reader is directed to this thorough discussion for details of the pathway.\textsuperscript{3} Stimuli from infectious agents as well as ischemic or other tissue injury lead to release of soluble TNF-α from multiple cell types in the myocardium, including macrophages, mast cells, endothelial cells, and fibroblasts. TNF receptor activation by TNF-α may have both beneficial and adverse consequences.\textsuperscript{22} In part, this may reflect regulation of downstream targets that are either proinflammatory\textsuperscript{23,24} or prosurvival.\textsuperscript{19,25–30} In addition to the well-
characterized gene expression programs regulated at the transcriptional level by NF-κB, there are multiple other avenues for cross-talk between inflammatory and survival signaling. For example, we have recently found that IKKβ, the critical kinase involved in NF-κB activation, regulates activation of the prosurvival kinase, Akt1, through a kinase-independent mechanism. Although beneficial effects of activation of the innate immune response in cardiomyocytes have been demonstrated in animal models, their deleterious effects also have been linked to myocardial dysfunction in heart failure, ischemia, and other states.

RIG-I

Single-strand and double-strand RNA in the cytoplasm are detected by members of the RIG-I–like receptor family (RIG-I, MDA5, and LGP2), also called helicases. Although not known to have a prominent part in cardiovascular pathophysiology, these molecules interact intimately with TLR-related and NF-κB–related signaling pathways; as such, they may become relevant in the setting of pharmacological intervention. RIG-I and MDA5 contain N-terminal caspase recruitment domains (CARD); activation leads to dimerization and downstream activation of mitochondrial antiviral signaling (MAVS) protein via these CARD. Activated MAVS induces phosphorylation of the transcription factor IFN regulatory factor-3 and recruits TRAF3 and TRAF6 to activate TBK1, IKKe, and the IKKα and IKKβ kinases, causing nuclear translocation of NF-κB with the attendant expression of numerous proinflammatory genes. Transcriptional activator proteins, including NF-κB, IFN regulatory factor-3, and IFN regulatory factor-7, assemble into a multi-protein complex that drives expression of interferon (IFN)-β. Activity of RIG-I and TRAF3 relies partly on ubiquitination.

RIG-I activation classically mediates the response to viral infection, which is encountered by the immune system as single-strand or double-strand RNA, or unmethylated double-strand DNA. Inflammatory signaling in response to virus infection leads to elaboration of type I IFN (IFN-α, IFN-β, IFN-κ) from the infected cells, which induces antiviral defenses in neighboring cells.

Single-strand and double-strand viral RNA in the endosomal compartment (ie, entering the cell through endocytosis, as opposed to cytoplasmic) is recognized by TLR3 and TLR7/8, or viral CpG DNA motifs activate TLR9. The recent review of innate immunity again provides a detailed description of TLR signaling in response to viral infection. MyD88-dependent signaling (TLR7, TLR8, and TLR9) involves recruitment of IRAK4, which phosphorylates and activates IRAK1. IRAK1 then activates TRAF6 and TRAF3, which activate IKK and TBK1, respectively. The MyD88-independent pathway (TLR3) involves recruitment of TRAF3 and TRAF6 by TRIF and subsequent activation of downstream kinases. In both cases, there is activation of the NF-κB proinflammatory gene program, as well as the production and release of type I IFN. This leads to activation of IFN-α/IFN-β receptors in neighboring cells, with activation of JAK1 and TYK2 and downstream activation of STAT1 and STAT2 transcription factors. STAT1 and STAT2 complex with IFN regulatory factor-9 to induce the expression of IFN-stimulated genes and the generation of the antiviral response.

Excessive or prolonged expression of IFNs is a cause of inflammatory damage in multiple tissues, and much has been learned about the regulatory mechanisms for controlling their production. The regulation of IFN-β expression in particular is well-studied. A small-molecule screen for inhibitors of IFN-β identified cardiac glycosides, which inhibit the sodium-potassium ATPase, leading to increased intracellular sodium concentration, which in turn inhibits the ATPase activity of RIG-I.

Negative regulation of these pathways is enacted at multiple levels. Deubiquitinating enzymes (DUBs) such as CYLD, DUBA, and A20 inhibit RIG-I and TRAF3 activity. Other inhibitors of the RIG-I or TLR pathways include MyD88s (spliced variant of MyD88), IRAK-M, and NLR family member X1 (NLRX1).

Cytokines

Cytokines are peptides or glycoproteins that are secreted locally in the heart or systemically in a broad range of cardiac conditions from heart failure and ischemia-reperfusion to myocarditis, allograft rejection, and sepsis-induced dysfunction. Leukocytes that migrate into the heart represent a major source of cytokines in most of these settings, but they are also secreted by virtually all the endogenous cell populations in the heart. Through binding their cognate receptors, cytokines have important effects on the extracellular matrix as well as the cardiomyocyte. The proinflammatory cytokines, TNFα, IL-1β, and IL-6, all play important roles in the heart. The overall impact on cardiac function depends on context as well as the level and duration of exposure, presence of coexpressed cytokines, and the cell machinery affected. Cytokines can modulate contractility directly through effects on excitation–contraction coupling, NOS3 activity, sphingomyelinase signaling, phospholipase A2 activity (arachidonic acid production), and β-adrenoreceptor sensitivity (a delayed effect). The signaling cascades activated by soluble TNFα are described. Some cytokines also have anti-inflammatory effects that may be beneficial in the heart. For example, after ischemia-reperfusion, the combination of cytokines and granulocyte colony-stimulating factor with stem cell factor or flt-3 ligand leads to limitation of infarct size and improvement in left ventricular function associated with mobilization of bone marrow stem cells to the myocardium.

The cytokine IL-18, expressed by cardiomyocytes, fibroblasts, endothelial cells, and vascular smooth muscle cells, is converted to its active form by caspase-1 and leads to production of other proinflammatory cytokines as well as matrix metalloproteinases. IL-18 expression in cardiomyocytes is transcriptionally regulated via NF-κB by extracellular matrix metalloproteinase inducer (EMMPRN), an integral membrane protein found in multiple cell types including cardiomyocytes. IL-18 is upregulated in models of cardiac ischemia-reperfusion and in patients with infarction, heart failure, and left ventricular hypertrophy. Overexpression of IL-18 in cardiomyocytes also induced activation of multiple transcription factors, including NF-κB and IFN regulatory
factor-I. Data increasingly support an important role of IL-18 in mediating aspects of adverse cardiac remodeling.

Chemoattractants are a subset of peptide cytokines originally identified as chemoattractants for leukocyte subsets. Recent work has identified unanticipated roles for these cytokines in many settings, including the heart. For example, SDF1 (CXCL12) and its receptor (CXCR4) appear to be important in myocardial repair at least in some settings, significantly modulating the engraftment and efficacy of intravenously infused progenitor cells after ischemic injury. Overexpression studies suggested SDF1-CXCR4 could have negative inotropic and proapoptotic effects in cardiomyocytes. However, cardiomyocyte-specific deletion of CXCR4 had no effect on baseline cardiac structure and function or the response to infarction. These results underscore the conceptual and technical differences in determining whether a pathway is necessary or sufficient for a specific effect and that these roles may differ among distinct target populations. MCP-1 is another chemokine that plays an important role particularly in monocyte recruitment and is induced in ischemic myocardium. In this series, Kolattukudy reviews growing evidence that MCP-1 has important additional effects in the heart beyond acting as a chemoattractant, at least in part, through the novel zinc-finger protein it induces, MCP-1–induced protein.

**Caspase-1 and the Inflammasome**

Caspase-1 (also called interleukin-converting enzyme) is an important modulator of cytokine signaling in response to stress. The primary role of caspase-1 is the activation of IL-1β and IL-18 from inactive precursors; it also induces production of IL-1α, IL-6, and TNF-α, and processes Bid to its active form, inducing the mitochondrial pathway of apoptosis. Caspase-1 is activated by caspase-11, which is itself activated in the setting of ischemia. Activation of caspase-1 involves complex formation with adaptor proteins via the caspase recruitment domain. Mice with deletion of caspase-1 showed mitigation of left ventricular remodeling after myocardial infarction. Mice with cardiac-specific over expression of inactive caspase-1 demonstrated no baseline phenotype but showed increased activation of caspase-1 and caspase-3 in the setting of endotoxin exposure or ischemia-reperfusion. After ischemia-reperfusion, the caspase-1–overexpressing hearts had greater infarct size and an exaggerated degree of apoptosis in myocardium remote from the infarct.

Immunology researchers have described a family of high-molecular-weight protein complexes known as the inflammasome, which converts procaspase-1 to caspase-1 in response to multiple stimuli. The reader is directed to recent reviews for a detailed description. In a manner analogous to TLR sensing of pathogen-associated molecular patterns and danger-associated molecular patterns, activation of the inflammasome is initiated by NOD-like receptors (NLR) that recognize intracellular structures common to microbes or cell-endogenous molecules. Activation is dependent on self-assembling scaffolding, typically including apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC). A subset of the NLRs effect pathways of the innate immune response distinct from inflammasome activation. These NLRs regulate multiple pathways in innate immunity, including NF-κB, mitogen-activated protein kinase, type I IFN, cytokines, chemokines, and reactive oxygen species. The inflammasome can be activated by cytoplasmic DNA, recognized by AIM2, with formation of a complex with ASC and procaspase-1, and can result in caspase-1 activation. Cytoplasmic RNA can activate the inflammasome via RIG-I, which complexes with ASC to activate caspase-1. A recent study in a myocardial ischemia-reperfusion model in mice deficient in caspase-1 or ASC demonstrated a role of inflammasome activation in the adverse sequelae: infarct formation, fibrosis, and cardiac dysfunction. Interestingly, these experiments suggest that inflammasome activation and IL-1β production occurred predominantly in cardiac fibroblasts rather than cardiomyocytes, followed by recruitment of bone marrow-derived cells.

**Cross-Talk With Other Signaling Pathways**

**Metabolic Signaling**

Numerous studies of the intersecting pathways that regulate cell metabolism and inflammation have illuminated their complex interplay. Efforts to target the inflammatory pathways for therapeutic intervention must confront the challenge that lies in this interdependence: that perturbations in one pathway can bear strongly on distantly related pathways, even those operating in different tissues. A brief discussion of some salient examples of metabolic-inflammatory cross-talk serves to illustrate this challenge.

Endogenous lipids, including fatty acids, have been shown to activate TLR4 signaling to mediate both inflammation and insulin resistance in adipose tissue. The metabolic effects paralleled activation of NF-κB, and both were significantly abrogated in TLR4–/– mice in response to lipid infusion. Lipopolysaccharide contains fatty acid moieties, which may account for the ability of TLR4 to mediate fatty acid signaling, although the majority of nutritional fatty acids are structurally distinct from the C12 lauric acid typically found in lipopolysaccharide.

The transcriptional coactivator, PPARγ-coactivator 1α (PGC-1α), controls expression of genes involved in mitochondrial energy homeostasis and plays a role in maintaining glucose homeostasis. PGC-1α knockout mice manifest mitochondrial dysfunction and increased susceptibility to heart failure. In a mouse model of skeletal muscle-specific deletion of PGC-1α, inflammatory signaling initiated in skeletal muscle led to elevated circulating levels of IL-6. Increased IL-6 was shown to modulate pancreatic islet β-cell insulin production, resulting in impaired glucose tolerance despite normal peripheral insulin sensitivity. PGC-1 signaling was also important in a lipopolysaccharide-induced model of sepsis, altered myocardial metabolism, and overt cardiac dysfunction associated with sepsis. In this model, PGC-1 gene expression was decreased in cardiomyocytes in an NF-κB activation-dependent manner. Combined, these data connect this master regulator of energy metabolism both upstream and downstream of major inflammatory signaling pathways.
AMP-activated protein kinase (AMPK) is a sensor of cellular energy status and a regulator of energy homeostasis and is pivotal in directing the cardiomyocyte response to multiple stressors including ischemia, hypoxia, glucose deprivation, and oxidative stress. On activation in response to elevated AMP/ATP ratio, AMPK engages multiple signaling intermediates, bearing on a variety of pathways involved in energy generation, protein synthesis, and ion channel activity. As a result, AMPK serves to coordinate a cell program in response to stress, broadly guiding conservation and replenishment of ATP, and prevention of cell injury and death. AMPK also has been found to be a point of regulation by other mediators, both cell-intrinsic and environmental. For example, AMPK is activated by the tumor suppressor LKB1 as well as the adipocyte-derived hormones adiponectin and leptin, and is inhibited by insulin. One important downstream mediator of AMPK activation is FGC-1a. Although recent studies have suggested alternate mechanisms, activation of AMPK is believed to be the primary mechanism of the beneficial effects of metformin treatment in diabetic patients.

AMPK may also be an important modulator of both innate and adaptive immunity. Studying AMPK signaling in macrophages, Yang et al. demonstrated that AMPK acts as a negative regulator of free fatty acid-induced inflammation. In a coculture experiment, inactivation of macrophage AMPK led to impaired adipocyte insulin sensitivity. Furthermore, the longevity-associated acetylase and sirtuin, SIRT-1, was identified as a mediator of the proposed anti-inflammatory effects of AMPK. AMPK has been shown to antagonize other TLR-mediated pathways, such as the TLR-mediated activation of dendritic cells from the resting state in response to environmental stimuli.

Survival Signaling
Inflammatory signaling also intersects with pathways controlling apoptosis, autophagy, and cell survival in many ways. Acute exposure of cardiomyocytes to lipopolysaccharide actually promotes cell survival and improved cardiomyocyte function (calcium handling/contractility) through TLR4 and IRAK1. The proinflammatory cytokine, macrophage migration inhibitory factor, is a proinflammatory cytokine that appears to have cardioprotective effects through AMPK and JNK signaling. NF-κB regulates transcription of inflammatory genes and many prosurvival factors. We have recently found that IKKβ, the dominant kinase leading to NF-κB activation, has important kinase-independent effects including regulation of the activation in vitro and in vivo of the prosurvival kinase, Akt1, in vascular endothelium. These examples are meant to illustrate the subtle and complex interactions of inflammatory and survival signaling that complicate efforts to exploit these pathways as therapeutic targets.

Therapeutic Implications
The recognition that inflammation can contribute to disease pathogenesis in a range of cardiac conditions has naturally prompted evaluation of the therapeutic potential of a range of anti-inflammatory approaches. Unfortunately, results in most settings have been disappointing. In acute myocardial infarction, despite promising results in animal models, antibodies to block leukocyte recruitment after reperfusion therapy were not beneficial in patients. In heart failure patients, despite extensive research suggesting a role for TNF-α in disease pathogenesis, anti-TNF-α therapy with etanercept or infliximab was also not beneficial and in some instances appeared deleterious. Although results have been somewhat more encouraging in specific subsets of pathogen-negative myocarditis patients, these results are from relatively small trials in which success is confined to surrogate or secondary endpoints. Thus, anti-inflammatory approaches have failed to demonstrate clinical benefit in multiple settings, despite a strong biological rationale and supportive data in preclinical models, as well as clinical pilot trials in some instances.

Whereas this experience sounds a cautionary note for those hoping to exploit anti-inflammatory approaches in heart disease, it is likely that multiple factors have contributed to these disappointing results and it may be premature to abandon an approach that may still hold promise. The inherent challenges and daunting process associated with pharmaceutical development undoubtedly apply to anti-inflammatory strategies as well. The majority of novel approaches fail despite promising preclinical data, partly reflecting the inadequacy of animal models and partly attributable to off-target effects. However, the duality of inflammatory signaling noted centuries ago may present a particular challenge in targeting these pathways that have beneficial and deleterious effects. At the least, such considerations likely narrow the therapeutic window and suggest that results will be highly context-dependent, underscoring the importance of patient and disease target selection.

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None.
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