Inflammasome Activation in Reperfusion Injury: New Links to Innate Immunity

Sebastian Grundmann, MD, PhD; Christoph Bode, MD; Martin Moser, MD

With the advances in percutaneous coronary intervention technology and accompanying medical therapy, the prognosis of patients with acute coronary syndromes has greatly improved over the last decades. Still, approximately 6% of admitted patients do not survive to hospital discharge, and despite the implementation of rapid interventional protocols, loss of cardiac tissue, and a consecutive decrease in cardiac function is the frequent consequence of acute myocardial infarction. In addition, increasing experimental and clinical evidence demonstrates that revascularization itself triggers a harmful inflammatory response, termed ischemia-reperfusion (I/R) injury, that might contribute up to 50% of the ultimate infarction area and that can exert deleterious effects even beyond the initially affected perfusion territory. Since the first description of I/R injury by Jennings et al in the 1960s, a large number of studies have aimed to unravel the basic mechanisms of this complex pathophysiological process. It became evident that I/R injury is an inflammatory-driven mechanism, in part depending on the infiltration of bone marrow-derived cells and the activation of classic inflammatory pathways. However, none of the experimental strategies has evolved into a clinically applicable adjuvant therapy for the treatment of acute coronary syndrome-patients, demonstrating the complexity of I/R injury.

The Inflammasome

The term “inflammasome” was coined to describe the cytosolic high molecular weight protein complex that mediates the activation of inflammatory caspses (especially caspase-1) and that ultimately results in the processing and secretion of the cytokines of the interleukin-1 family. The suffix “-some” was chosen in analogy to another well-known caspase-activating complex, the apoptosome, with which the inflammasome shares functional and structural similarities. So far, 4 prototypes of inflammasomes have been described: the NALP1 inflammasome, the NALP3 inflammasome, the IPAF inflammasome, and, recently, the AIM2 inflammasome. Whereas the NALP-inflammasomes are characterized by cytoplasmic receptors of the NACHT-domain leucine-rich repeat protein family and activate caspase-1 via the adaptor molecule apoptosis-associated speck-like protein containing caspase recruitment domain, the IPAF-inflammasome is able to directly recruit caspase-1 via interaction of the caspase-associated recruitment domains. Inflammasomes are assembled by self-oligomerizing scaffold proteins and function as central mediators of inflammatory immune response triggered by danger-associated molecular patterns and danger-associated molecular patterns. Until now, they have been best studied in bone marrow-derived cells of the myeloid lineage, but inflammasome components are expressed in a wide variety of cell types. The AIM2 inflammasome was recently identified as the first non-NOD like receptor family member able to form an inflammasome scaffold, and the future identification of additional inflammasome-structures is likely.

Recently, different components of the innate immune system, the evolutionarily ancient defense mechanism against exogenous pathogens and endogenous danger signals, were implicated in this context. In this issue of Circulation, Kawaguchi and coworkers from the Shinshu School of Medicine and the Jichi Medical University in Japan present comprehensive experimental data that demonstrate a critical role of the inflammasome in cardiac fibroblasts for myocardial I/R injury.

The findings now presented by Kawaguchi and coworkers are important for 2 reasons: first, their paper is the first study to directly link inflammasome activation to myocardial ischemia-reperfusion injury, and second, it is another piece in the puzzle that suggests the critical role of cardiac fibroblasts in cardiac disease.

Several other reports in the field had demonstrated an important, harmful role of the innate immune system in this context, and the activation, regulation, and efficacy of the inflammasome have been described to a great extent regarding to pathogen control and auto-immune disease. The present study elegantly transfers this knowledge from basic immunology to a new field of research with great clinical impact. The authors demonstrate a harmful, inflammasome-dependent mechanism of ischemia-reperfusion injury that makes perfect pathophysiological sense: the rapid initiation of a sterile inflammatory response by the release of endogenous danger signals. They propose a mechanism by which the production of reactive oxygen species and the efflux of potassium ions in cardiac fibroblasts result in inflammasome activation in these cells and, eventually, in the activation of interleukin-1beta, subsequently recruiting bone-marrow-
derived cells to the site of injury that sustain the inflammatory response. Although the initially activated receptor is not identified, the authors use genetically-deficient mice and bone marrow chimeras to demonstrate the importance of acute coronary syndrome and caspase-1 for myocardial infarction development, fibrosis, and the deterioration of cardiac function.

The Fibroblast: The Long-Neglected Neighbor in the Cardiac Community

This study by Kawaguchi et al is another addition to an increasing amount of evidence that stresses the importance of cardiac fibroblasts for cardiovascular pathology. This cell population comprises up to two-thirds of all cardiac cells, but has long been neglected with regard to physiological and pathophysiological functions besides cardiac fibrosis and remodeling. It now becomes increasingly evident that even the healthy heart fibroblasts are not just inactive bystanders that watch the cardiomyocytes do the real work, but that they interact with the other cardiac cell populations by paracrine mechanisms, alterations in extracellular matrix composition, and direct cell-cell contact. The authors of the present study show that these cells are an integral part of the early inflammatory response to ischemia-reperfusion injury, at a time point even before the infiltration of bone marrow-derived cells takes place. Hypoxia-reoxygenation experiments induced inflammasome activation in cardiac fibroblasts but not in cardiomyocytes. Moreover the lipopolysaccharide-induced secretion of interleukin-1beta is attenuated in cardiac fibroblasts from apoptosis-associated speck-like protein containing caspase recruitment domain-deficient mice. This is therefore another study in which the fibroblasts eventually turn out to be the crucial cell population in a pathophysiological process—an increasing trend in cardiovascular publications over the past few years.

Obstacles and Problems on the Way to Clinical Practice

Despite the elegant study design, several important limitations of the work by Kawaguchi et al need to be taken into account: although the innate immune system is an evolutionarily old defense mechanism with a relatively high degree of conservation among mammalian species, the mechanisms of inflammasome activation differ between mice and humans. For example, the inflammasome-interacting protein CARDINAL, which facilitates caspase-1 recruitment for NALPs without an intrinsic caspase-associated-recruitment-domain, is not present in the mouse genome at all, and even among primates the innate immune response to endogenous and exogenous activators shows a lineage-specific divergence.

It should also be noted that the role of inflammation in the myoccardial response to ischemia reperfusion injury is more ambivalent than the first impression may suggest, and that the bidirectional role of inflammatory signaling extends far beyond the mentioned inflammatory cytokine TNF-α. Timmers et al reported in a past issue of Circulation that specific inhibition of the inflammatory cyclooxygenase COX2 results surprisingly in an increase in mortality in a porcine model of acute myocardial infarction, probably due to decreased collagen fiber density in the infarct area and to increased myocardial rupture. Again, the cell population responsible for this phenotype were the cardiac fibroblasts.

Moreover, the manuscript leaves ample room for additional and more specific studies. As mentioned above, at least 4 different prototypes of inflammasome-scaffolds exist, and the specific importance of the individual ones remains to be investigated. In addition, the study sets a focus on the downstream components and signaling events after inflammasome activation by reactive oxygen species, whereas the responsible receptor, most likely of the NOD-like receptor family, is not identified. These questions will be of critical importance for the potential future development of inflammasome-targeting treatment strategies. So far, the repertoire of pharmacological agents that could utilize our new understanding of the innate immune response seems limited. Only interleukin-1 inhibitors and the respective receptor blockers have progressed toward clinical applicability for inflammatory diseases such as rheumatoid arthritis.

Collectively, our recently gained insights on the innate immune system suggest a function way beyond the initially assumed first defense line to guard the “self” of the host-organism from the “nonself” of the environment. Very probably, the near future will yield more evidence that the individual components of this system form a complex sensor network to detect the heterogeneous manifestations of “danger,” may they come from an invading pathogen or a clogged artery and subsequent tissue ischemia. There may be some cases in which the initiated response to the detected danger may do additional harm, urging us to search for a chain to restrain our helpful guard. However, the right metal to forge this chain remains yet to be discovered.

Disclosures

None.

References


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