Amplified Bioactive Signaling and Proteolytic Enzymes Following Ischemia Reperfusion and Aging
Remodeling Pathways That Are Not Like a Fine Wine

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Left ventricular (LV) remodeling, defined as changes in myocardial structure and geometry, is considered to be a fundamental milestone in the progression to heart failure. This is particularly true in the clinical context of a myocardial infarction (MI), whereby adverse LV remodeling is directly associated with the progression to heart failure and increased morbidity and mortality. LV remodeling is a multifactorial process that includes changes within the myocardial, vascular and extracellular matrix (ECM). However, in terms of post-MI remodeling, changes in myocardial growth/viability and ECM structure/composition are ubiquitous events, and they occur in a heterogeneous fashion within the remote viable myocardium, the myocardial region surrounding the MI (border zone), and the MI scar itself. It is the summation of the alterations within both the cellular and extracellular compartments, which occur in all these regions post-MI, that promulgates adverse LV remodeling and ultimately the progression to heart failure. Through the use of animal models and clinical translational studies, certain signaling and proteolytic events have been identified to uniformly occur following an MI and to likely induce the cascade of events that yield changes in myocardial structure and function. In this issue of Circulation, Jugdutt and colleagues report on how the activation of a specific signaling pathway, the angiotensin-II receptor, influences a number of critical cellular signaling and ECM proteolytic events that can contribute to adverse LV remodeling. These investigators examined a number of critical pathways following a period of ischemia and reperfusion that resulted in a significant and relevant MI. These investigators not only examined these signaling/proteolytic events in a clinically-relevant model of MI, but, more importantly, they examined the post-MI remodeling process within the aging myocardium. The findings from this study are important for two reasons. Firstly, this study clearly demonstrated that important interactions occurred between the angiotensin-II receptor and the induction of bioactive molecules and proteases following an acute MI. Secondly, this study demonstrated that an amplified response occurs between these intersecting pathways within the aging myocardium following an acute MI. Taken together, the findings by Jugdutt and colleagues provide mechanistic evidence that the elderly myocardium is a more vulnerable substrate to an ischemic insult, and that this is likely due to enhanced/amplified induction of signaling cascades and proteolytic events that would directly contribute to a more advanced and accelerated LV remodeling process.

Myocardial Cell Death Following MI and With Aging

Myocyte loss following MI can occur through 3 different mechanisms: necrosis, apoptosis and defects in autophagy. While the first mechanism contributes to acute and significant loss of viable myocytes, it is likely that these other pathways contribute to continued myocyte cell death long after the acute event and can also contribute to progressive LV remodeling. Alterations in apoptosis and autophagy have been identified with aging, which would lead to the hypothesis that the aging myocardium, when subjected to a similar stress/insult, is more susceptible to adverse LV remodeling than the young myocardium. Indeed, an initial proteomic approach in aging mice identified alterations in levels of critical proteins involved in modulating oxidative stress. Jugdutt and colleagues identified that inducible nitric oxide synthase was robustly increased within the aging myocardium following an acute MI, which was paralleled by an induction of inflammatory mediators such as interleukin-6 and tumor necrosis factor. In these studies, infusion of an angiotensin-II receptor antagonist at the time of reperfusion significantly reduced these markers of oxidative stress and cytokine activation. Whether and to what degree the infusion of an angiotensin-II receptor antagonist at the time of the initial MI would prevent myocyte loss/remodeling through mediating apoptotic/autophagic pathways, and in turn cause a long-term favorable effect on LV remodeling, remains to be established. Nevertheless, this large animal model provides additional evidence that a “priming effect” exists within the senescent myocardium that would cause a robust increase in signaling pathways that contribute to adverse LV remodeling.

Myocardial ECM Following MI and With Aging

Degradation of the ECM following the acute phase of an MI is considered to be an essential event that allows for the ingress of inflammatory cells and the proliferation and...
maturation of macrophages and fibroblasts. It also provides the necessary substructure for scar formation. In the early part of the 20th century, it was identified that early (within 24 hours) after an MI, degradation of the normal collagen matrix occurred, which was then followed by significant matrix deposition. It is now recognized that the myocardial ECM is a complex microenvironment containing a large portfolio of matrix proteins, signaling molecules, proteases, and cell types that play a fundamental role in the post-MI remodeling process. In terms of the structure and composition of the ECM, a hallmark feature of the aging myocardium is increased collagen accumulation, which in turn impairs myocardial compliance and diastolic function. With respect to ECM signaling molecules, a pleiotropic bioactive molecule that plays a predominant role in the regulation of ECM synthesis is transforming growth factor (TGF). Alterations in TGF, osteopontin (OPN), integrins, and extracellular matrix proteins that regulate ECM structure (such as SPARC [secreted protein acidic and rich in cysteine]), proteases, and inhibitors (such as MMPs and SLPI). Under normal conditions, dynamic and likely continuous interactions between prototypical receptors such as the angiotensin-II receptor to profibrotic and matricellular proteins and the proteolytic enzymes determine the homeostatic balance of the ECM. The study in this issue of Circulation by Jugdutt and colleagues demonstrated that a shift in the balance if this system occurs within the aging myocardium, which would likely favor a more aggressive and amplified remodeling response following an acute MI. Following an acute MI, the release of cytokines such as interleukin-6 (IL-6) occurred, which was associated with an induction of TGF, OPN, and an array of proteolytic enzymes including MMPs (ie, MMP-2, MMP-9) as well as SLPI, many of which are likely released/induced by an acute inflammatory cell response. Jugdutt and colleagues demonstrated that this cytokine/matrix/kine/proteolytic cascade could be modified with an infusion of an angiotensin-II receptor antagonist.

In addition to the stimulation of prosynthetic ECM pathways following an MI, the induction, activation and release of ECM proteolytic enzymes occur. These include serine proteases, matrix metalloproteinases (MMPs) and a-disintegrin and metalloproteinases. With respect to the MMPs, this constitutes a large family of proteolytic enzymes, and while the role of each of these MMPs is just beginning to be elucidated, a signature of certain MMP types appears to be released following an acute MI in patients. This includes the soluble MMP types MMP-2 and MMP-9.3,7 While the predominant pathway for MMP-2 activation is likely through another MMP type, the membrane type-1 MMP,3 an alternative activation mechanism that is likely to be operative in the context of acute tissue injury and inflammation, is through proteolytic processing by serine proteases. Inflammatory cells, such as macrophages and neutrophils, release certain MMP types, including MMP-9, serine proteases, and inhibitors of serine proteases, such as the secretory leukocyte protease inhibitor (SLPI).3 In past animal studies, it has been shown that SLPI can terminate the acute inflammatory mediated proteolytic response and facilitate wound healing.3 In the study by Jugdutt and colleagues, increased levels of proteolytic enzymes such as a-disintegrin and metalloproteinase-10,
a-disintegrin and metalloproteinase-17, and MMP-2, as well as SLPI, were reported in the aging myocardium, and in turn would likely yield alterations in ECM homeostasis under steady state conditions as well as following acute MI.

Aging, Myocardial Remodeling and Basic Research: A Paradox

Cardiovascular disease, in particular, ischemic heart disease, is a function of age, where the incidence increases in almost an exponential fashion following the fifth decade of life. Clinically, it is well-recognized that elderly patients can be at much higher risk for LV remodeling and the progression to heart failure, despite an equivalent initial MI size when compared to younger cohorts of patients. The preponderance of basic research over the past decade, in terms of mechanisms and pathways that promulgate LV remodeling post-MI, have been performed in young mice using transgenic approaches. However, biological signaling pathways, proteolytic portfolios, and the overall response to myocardial injury can be quite different in these small, young rodent when compared to larger mammals. While these murine studies have provided invaluable insight and provoked new hypotheses, they must be carried forward through the use of large animals that more closely recapitulate the clinically-relevant context. Judgutt and colleagues used a large animal model of aging and MI that demonstrated the complexity of the ECM with respect to being a reservoir for bioactive molecules, matrines, and proteases, which are in a constant and dynamic balance (Figure); one that is likely to be much different within the aging myocardium. Unfortunately, the balance in these signaling/proteolytic pathways within the aging myocardium appears to be one that would favor a more aggressive and amplified adverse LV remodeling response following a myocardial insult.

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References


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