ICE-ing the Heart

Roberta Gottlieb

In this issue of Circulation Research, Syed et al report that overexpression of caspase-1 (ICE) contributes to myocardial ischemia/reperfusion injury. Transgenic mice were generated using the alpha-myosin heavy chain promoter to drive caspase-1 expression in the heart. The mice expressed caspase-1 30-fold more than the nontransgenics. Despite this massive overexpression, no spontaneous caspase activation or apoptosis was noted, and there was no apparent cardiac phenotype. However, endotoxin exposure and ischemia/reperfusion were associated with increased caspase-1 and -3 activation in the transgenic mice, suggesting that caspase-1 contributes to myocardial pathology in these settings. Culture studies were used to bolster the notion that caspase-1 activated caspase-3 directly rather than through upstream caspases.

Missing from this study was any analysis of cytokine processing, although the primary role of caspase-1 is to process interleukin-1-beta (IL-1β) and IL-18, and potentially IL-1α, IL-6, and tumor necrosis factor alpha-α (TNF-α). Enhanced caspase-1 activity and IL-18 have been reported after myocardial infarction, suggesting a role for caspase-1 in posts ischemic inflammation and injury.2 Frantz et al who showed that targeted deletion of caspase-1 was associated with reduced postoperative mortality and less left ventricular failure, in which inflammatory processes and low levels of ongoing cell death prevail.

Whether the caspase-1-dependent apoptosis after ischemia is due to extracellular signaling by the processed cytokines or to intracellular events (caspase-1 activation of caspase-3) remains an open question. The cellular studies conducted by Syed et al show that in procaspase-1 transfected cells subjected to hypoxia, there was caspase-3 cleavage in the absence of processing of caspase-8 or -9, which they argue reflects direct activation of caspase-3 by caspase-1. However, it is now widely recognized that caspase-8 and -9 can be active in the absence of proteolytic processing, and that ‘downstream’ caspases, however they become activated, can proteolytically process the initiator caspases. Thus it is difficult to infer activation of caspase-8 or -9 from the demonstration of proteolytic fragments.10 Caspase-1 has been shown to process Bid to its active form, thereby activating the mitochondrial pathway of apoptosis.11 Subsequent work showed that this pathway could be initiated in neuronal cells subjected to ischemia.12 Bid is well known to act as a protease sensor, and can respond to initiator caspases, Granzyme B, cathepsins, and calpains.13,14 Work by Kitsis et al showed marked infarct size reductions in Bid-null mice, pointing to the importance of this mediator regardless of the upstream protease.15

An additional consideration is whether caspase-1 enzymatic activity is required for initiation of apoptosis in this setting. It was shown by Lamkanfi et al16 that caspase-1 could activate NF-κB in the absence of protease activity. Given the controversial roles of NF-κB signaling in the ischemic and reperfused heart,17,18 future studies using a catalytically inactive mutant of caspase-1 will provide important mechanistic insights.

What does this study tell us about the role of caspase-1 in the myocardium? Overexpression of caspase-1 allowed the investigators to convincingly demonstrate that endotoxin exposure and ischemia can lead to processing of caspase-3. However, such an overexpression study cannot provide in-

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Caspase-1 can complex with and be activated by a variety of regulators to process interleukins or activate apoptosis. Activation of NFκB by caspase-1 does not require enzymatic activity but does require RIP2. Members of the inflammasome family that participate in interleukin processing are shown with double lines. Negative regulators Pseudo-ICE and ICEBERG may bind to RIP2 or caspase-1 itself. Whether these negative regulators can interfere with the inflammasome or caspase-1 activation by caspase-11 is unknown. Additional regulators are likely to exist. It is also unknown whether the composition of the caspase-1 complex determines the preferred substrates.

It is clear that caspase activation—including caspase-1—can lead to apoptosis in the myocardium, but the relative contribution of caspase-dependent cell death to tissue loss after ischemia/reperfusion is less clear. Targeted deletions of caspases can provide some insight, such as the work by Frantz et al in the caspase-1 knockout mouse. Inhibition of apoptosis by overexpression of a caspase-9-dominant negative, Bcl-2, or Akt have also been shown to reduce infarct size by 50% to 70%. To the extent that calcium overload and oxidative damage mediate ‘necrotic’ cell death, Bcl-2 and Akt may also protect against necrosis, perhaps explaining why a greater protective effect is seen with these agents than with caspase inhibitors, which have been shown to reduce infarct size by at most 20% to 50%. Moreover, in some settings, caspase inhibition merely serves to convert apoptosis to necrosis. Finally, because apoptosis is associated with mitochondrial dysfunction, caspase inhibition may not be sufficient to salvage the energetically needy cardiomyocyte.

This study demonstrates that cardiomyocytes can respond to caspase-1 overexpression and its subsequent activation by initiating apoptosis. Caspase-1 can interact with multiple inflammatory and apoptotic pathways (see Figure). However, further work will be required to determine the extent to which endogenous levels of caspase-1 contribute to myocardial cell death after ischemia, and whether this proceeds via a cytochrome-dependent pathway or via cell-autonomous processes. Finally, the role of caspase-1—and its negative regulators—in heart failure, where cytokines are acknowledged to play an important role, merits a closer look.

References


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