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CAN ARC SAVE THE HEART?

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Ekhterae and colleagues present their findings regarding cardiomyocyte apoptosis, myocardial remodeling, and activation of the Apoptosis Repressor with Caspase Recruitment Domain (ARC) following coronary artery ligation in sheep. Currently, ARC is believed to be expressed almost exclusively in the heart and skeletal muscle, and activation of ARC is known to inhibit apoptosis [1]. Previously, Donath et al. observed that ARC deficient mice developed cardiomyopathy more rapidly than littermate controls after aortic banding. These deficient mice also had larger infarcts after ischemia/reperfusion injury (I/R). Both observations were associated with increased cardiomyocyte apoptosis [2]. Therefore to further elaborate on the temporal associations of ARC with respect to myocardial remodeling, Ekhterae and associates induced apical infarcts in sheep and obtained functional data by 2D echo at two, eight and 32 weeks post ligation. Concurrent biopsies were taken from the infarct border zone and a remote region. These biopsies were used to assess ARC activation and measure apoptosis.

In this experimental model of myocardial infarction (MI), the left ventricular ejection fraction (EF) decreased between two and eight weeks post ligation from 32% to 17% respectively. As might be expected, the end systolic volume (ESV) was increased by a factor of 1.5 x baseline at two weeks and 2 x baseline at eight weeks indicating that adverse ventricular remodeling was occurring. Similarly cardiomyocyte apoptosis was evident at two weeks and continued to increase at the eight week measurement. By 32 weeks the EF and ESV had not changed significantly from eight weeks, and apoptosis was decreasing. Interestingly, activated ARC was elevated at two weeks, diminished at eight weeks and increased again at 32 weeks in the border zone. Certainly one could argue that if total ARC levels were decreased at eight weeks as compared to two and 32 weeks there may be a consumption or production issue. However, total ARC levels were not significantly different in the borderzone. Thus decreased levels of activated ARC may be linked to ventricular remodeling and myocyte death. These correlations are further supported by caspase-3 and BAX levels. Both proteins are associated with apoptosis, and the levels of both were inversely related to the level of activated ARC.

This study leads to the obvious question--if low levels of activated ARC are linked to cardiomyocyte death and negative remodeling, will increasing levels of activated ARC improve outcomes such as the progression to heart failure following MI? Chatterjee and

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associates noted that rabbits transfected with the ARC gene produced significantly higher levels of ARC protein compared to the null vector group at six weeks post-transfection. Following I/R the rabbits overexpressing ARC had higher EFs at four and six weeks post-I/R and improved preservation of left ventricular geometry [3]. Chatterjee's data supports the concept that increasing levels of ARC may be of therapeutic benefit. It is equally important to consider the role of exogenous ARC administration which may clinically be the easiest to deliver. Gustafsson et al. infused the ARC protein linked to TAT (Trans-Activator of Transcription) into rat hearts using the isolated heart system (Langendorff). TAT contains a domain that facilitates protein transduction across the cell membrane. The TAT-ARC fusion protein successfully transduced into the heart tissue and was associated with smaller infarct sizes following I/R [4]. In addition to the use of fusion protein such as TAT-ARC, manipulation of the intracellular pathways leading to ARC production or activation may be a third option. Tan et al. recently demonstrated that myocardial ARC can be deactivated by calcineurin [5]. Therefore, calcineurin inhibitors may be another method of manipulating levels of ARC following myocardial injury.

Given the existing data, it is clear that ARC will be of increasing interest to clinicians and scientists involved with myocardial ischemia and heart failure research. Dr. Gorman's group has revealed another piece of the puzzle regarding ARC.

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