Late Breaking Science: Linking Genes to Function in the Heart and Vasculature

BASIC ABSTRACTS

Exogenous Hematopoietic Stem Cells Can Regenerate Infarcted Myocardium

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To determine whether hematopoietic stem cells (HSC) can transform into cardiomyocytes with the potential to repair dead myocardium after infarction, Lin+/c-kit+ HSC were harvested from transgenic mice expressing green fluorescent protein (GFP) and injected in the region bordering the infarct–3, 6- and 30-day post-infarct timepoints. Approximately 30% of the injected HSC expressed GFP and were detected for the duration of the observation period. These results indicate that HSC can participate in the repair of infarcted myocardium in vivo.

Mutations in the Human β-Sarcoglycan Gene in Familial and Sporadic Dilated Cardiomyopathy, a Disease of the Cytoskeleton and Sarcolemma

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Background: Dilated cardiomyopathy (DCM) is a significant cause of morbidity and mortality due to congestive heart failure and rhythm abnormalities. Approximately 30% of cases are familial, with the remainder occurring sporadically. Autosomal dominance is the most common form of DCM, although X-linked disease is also well described. Two genes have been identified for the X-linked forms (dystrophin and tafazzin), whereas three genes have been identified in autosomal dominant DCM (actin, lamin A/C, desmin). We have hypothesized that DCM is a disease of the cytoskeleton and sarcolemma and have focused our studies on cardiac proteins whose products are found in both the cytoskeleton and sarcolemma. As an example, we report the screening of a β-sarcoglycan, a member of the dystrophin-associated protein complex (DAPC).

Results: Mutation analysis of the DCM pedigree identified a single nucleotide change in exon 8 of the β-sarcoglycan causing an amino acid change from a polar (serine) to nonpolar amino acid (alanine) altering the protein secondary structure. This mutation results in a premature stop codon and is predicted to result in a protein truncated at the N-terminus and lacking a portion of the cytoskeletal domain. The truncated protein is predicted to have a shorter than normal half-life, which would result in markedly reduced expression in the heart.

Conclusion: Mutations in the β-sarcoglycan gene causes autosomal dominant DCM. As mutations of this gene are also known to cause the Syrian hamster cardiomyopathy, this strongly suggests that DCM results from disruption of the cytoskeleton/sarcolemma.

Dual Modulation of Cell Survival and Cell Death by β2-Adrenergic Gi and Gs Signaling in Adult Mouse Cardiac Myocytes

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Cardiac β2-AR activates both GS and Gi proteins whereas β1-AR couples only to Gi. The goal of this study is to determine whether β1-AR and β2-AR differ in regulating cardiomyocyte survival and apoptosis, if so, to explore underlying mechanisms. To avoid complicated crosstalks between β-AR subtypes, we express β1-AR or β2-AR individually in the null background, Tg(β1-AR) and Tg(β2-AR) double knockout mice, respectively. Using adult mouse myocyte culture and adenoviral gene transfer techniques, stimulation of β1-AR, but not β2-AR, markedly induces myocyte apoptosis, as indicated by increased TUNEL or Hoechst staining positive cells and DNA fragmentation. Inhibition Gi signaling with pertussis toxin converts β2-AR to β1-AR in terms of its apoptotic effect, suggesting that Gi is essential for β2-AR-mediated cell survival. On the other hand, β1-AR mediated cell death is blocked by agonist activation of Gi/o or PKA, or by over-expression of Akt, a powerful survival signal, this finding is fully abolished by inhibition of Gi with pertussis toxin, scavenging Gβγ with Y185R-kct, or blocking PKA with LY294002, indicating that β2-AR activates Akt via Giβγ-PISK pathway. The significantly different effects of β-AR subtypes on cardiac cell survival and apoptosis may have important pathophysiological and therapeutic implications in chronic heart failure.
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