There is considerable debate about the choice of intravenous platelet glycoprotein IIb/IIIa inhibitors for percutaneous coronary intervention, after a meta-analysis of 7 trials and 16,771 patients has shown a 38% reduction in death or non-fatal MI 30 days after the index procedure. At 149 hospitals in 18 countries throughout North America, Europe, and Australia, 4810 patients were randomized between 135 000 and 85 000 IU of abciximab or an abciximab on a double-blind, double dummy basis. Clopidogrel and aspirin were administered preprocedure, along with a 70 U/kg intravenous heparin bolus. The dose of tirofiban was 10 mcg/kg/min and 0.125 mcg/kg/min infusion for 18–24 hrs; for abciximab it was 0.25 mcg/kg bolus and 0.125 mcg/kg/min infusion. Patients qualified by having had a past history of MI or unstable angina with criteria for “intent-to-study” lesions addressed by percutaneous revascularization, and were not with evolving ST-elevation MI or with serum creatinine >2.5 mg/dl. The primary endpoint is 30 day death or non-fatal MI and the trial has 80% power to determine non-inferiority for the EPS1TEN trial. The primary endpoint data will be presented along with the key subgroups such as diabetics. Follow-up data for the trial to 1 year will also be performed.

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, 3–5 hrs after coronary artery occlusion in mice. A band of closely packed cells was identified within 17 days in nearly 50% of HSC injected hearts, between the endocardial and epicardial surface of the infarcted ventricle. This band occupied 50% of the damaged portion of the wall. c-kit+/GFP positive HSC were found in the infarcted area shortly after coronary ligation and were still detectable at 7 days, c-kit stained HSC were not labeled by markers of myocytes, a-sarcomeric actin and myosin, endothelial cells, factor VIII, and smooth muscle cells, smooth muscle actin. The band of tissue included in the infarcted zone was constituted 75% by GFP, a-sarcomeric actin, myosin and a-actin positive cardiac muscle cells. Other GFP-positive cell populations were endothelial cells and smooth muscle cells, organized in nascent capillary structures and arterioles. Proliferating myocytes were detected in the heart, partially myoblasts and resembled late fetal-neonatal cells. GFP-positive replicating myocytes, endothelial cells and smooth muscle cells were c-kit negative. Infarcted mice were injected with BrdU, once a day for 4 days, to establish the extent of cell proliferation in the regenerating myocardium: 28% myocytes, 17% endothelial cells and 12% smooth muscle cells were BrdU positive. These three levels of BrdU labeling were statistically different. Additionally, the percentages of cells positive to Ki67 were measured to evaluate the fraction of cycling cells in this small population: 18% myocytes, 10% endothelial cells and 8% smooth muscle cells were in G1, S, G2 in conclusion, HSC, when injected in the heart, rapidly differentiate into myocardium resulting in significant recovery of muscle mass after infarction.

Mutations in the R1aα Regulatory Subunit of Protein Kinase A Cause Familial Cardiac Myxomas

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Dilated cardiomyopathy (DCM) is a significant cause of morbidity and mortality Background: DCM is a disease of the cytoskeleton and sarcolemma and have focused our studies on cardiac involvement whose products are found in these structures. Here we report the screening of a-sarcomeric myosin, a member of the dystrophin-associated protein complex (DAPC). Methods: Blood was drawn and DNA extracted from one 4-generation family and 50 sporadic cases of DCM after informed consent. Cardiac samples were obtained after transplantation or autopsy. The d-sarcomeric gene was screened for mutations using single strand conformation polymorphism (SSCP), denaturing high performance liquid chromatography (DHPLC) and MALDI mass spectrometry. 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 DFM (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 involvement whose products are found in these structures. Here we report the screening of a-sarcomeric myosin, a member of the dystrophin-associated protein complex (DAPC). Results: Mutation analysis of the DCM pedigrees identified a single nucleotide change in exon 8 of d-sarcomeric causing an amino acid change from a polar (serine) to nonpolar amino acid (alanine) altering the protein secondary structure. In 2 of the 50 sporadic cases, a 3bp deletion in exon 9, which deletes lysine at position 238, occurred. Neither the missense mutation nor deletion mutation was seen in 200 control patients. Immunohistochemistry demonstrated significant reduction of d-sarcomeric staining. Conclusions: Mutation of the d-sarcomeric gene causes autosomal dominant DCM. As of this review, three of these mutant genes have been identified which cause the Syrian hamster cardiac myopathy as well as human limb girdle muscular dystrophy, it appears that mutations in this gene place patients at risk for a spectrum of clinical features ranging from cardiomyopathy to skeletal myopathy. This is similar to other DAPC members and dystrophin itself, supporting our final common pathway hypothesis which suggests that DCM arises from disruption of the cytoskeleton/sarcolemma, indicating that mutations in this gene place patients at risk for a spectrum of clinical features ranging from cardiomyopathy to skeletal myopathy. This is similar to other DAPC members and dystrophin itself, supporting our final common pathway hypothesis which suggests that DCM arises from disruption of the cytoskeleton/sarcolemma, indicating that mutations in this gene place patients at risk for a spectrum of clinical features ranging from cardiomyopathy to skeletal myopathy.

Dilated 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 coupling only to Gs. The goal of this study is to determine whether β1-AR and β2-AR differ in regulating cardiocyte 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, β2-Adrenergic Gi and Gs Signaling in Adult Mouse Cardiac Myocytes background, β1-2 double knockout mouse cardiomyocytes. Using adult mouse heart and adenovirus gene transfer and adenovirus gene transfer and adenovirus 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 survival effects. To explore the downstream signaling events of β2-AR couples Gi, we first examined the possible involvement of a role of p38 MAPK in β2-AR-mediated cell survival. In contrast, β2-AR (but not β1-AR) elevates the activity of Akt, a powerful survival signal; this effect is fully abolished by inhibiting Gi with pertussis toxin, scavenging Gβγ with JARK-βγ, or blocking PI3K with LY294002, indicating that β2-AR activates Akt via Gβγ/PI3K pathway. Most importantly, inhibition of the Gβγ-PI3K-Akt pathway converts β2-AR signaling from survival to apoptotic. Thus, β2-AR, unlike β1-AR, activates concurrent apoptotic and survival signals in cardiomyocytes, and the survival effect is mediated by the Gβγ/PI3K-Akt pathway. The strikingly 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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