TARGET: Do Tirofiban And ReoPro Give Similar Efficacy Trial?

Eric J. Topol et al

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 16,770 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 12/30/99 and 8/25/00 and treated with either tirofiban or abciximab on a double-blind, double dummy basis. Clopidogrel and aspirin were administered pre-procedurally, along with a 70 U/kg intravenous heparin bolus. The dose of tirofiban was 10 mg/kg bolus and 0.15 mg/kg/min infusion for 18–24 hrs; for abciximab it was 0.25 mg/kg bolus and 0.125 mg/kg/min (max 10 mg/min) infusion. Patients qualified by history of angina for "intent-to-stent" lesions addressed by percutaneous revascularization, and were randomized between 12/30/99 and 8/25/00 and treated with either tirofiban or abciximab on a double-blind, double dummy basis. Clopidogrel and aspirin were administered pre-procedurally, along with a 70 U/kg intravenous heparin bolus. The dose of tirofiban was 10 mg/kg bolus and 0.15 mg/kg/min infusion for 18–24 hrs; for abciximab it was 0.25 mg/kg bolus and 0.125 mg/kg/min (max 10 mg/min) infusion. Patients qualified by history of angina for "intent-to-stent" lesions addressed by percutaneous revascularization, and were non-inferior for the primary endpoint of death or non-fatal MI 30 days after the index procedure.

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

BASIC ABSTRACT

Exogenous Hematopoietic Stem Cells Can Regenerate Infarcted Myocardium

Donald Oric, Jan Kajstura, Stefano Chimenti, Baozhong Li, Stacie Anderson, David Bodine, James Pickel, Cannan Joshi, Joseph Frangiosi, Francis Arriens, New York Medical College, Valhalla, NY. National Institutes of Health, Bethesda, MD.

To determine whether hematopoietic stem cells (HSC) can transform into cardiomyocytes with the potential to repair dead myocardium after infarction, Lin-Kit+ HSC were harvested from transgenic mice expressing green fluorescent protein (GFP) and injected in the region bordering the infarct, 3–5 hours after coronary artery occlusion in mice. A band of well-packed cells was identified at 17 days in nearly 5% of the 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 marking with myosin, α-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, α-sarcomeric actin, myosin and α-actinin 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 partially aligned with myofibrils and resembled late fetal-neonatal cells. GFP-positive replicating cells were labeled 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 set of repair: 18% myocytes, 10% endothelial cells and 8% smooth muscle cells were in G1, G2, M. In conclusion, HSC, when injected in the heart, rapidly differentiate into myocardium resulting in significant recovery of muscle mass after infarction.

Mutations in the R1α regulatory Subunit of Protein Kinase A Cause Familial Cardiac Myxomas

Carl J. Vaughan, Martin Casey, Je He, Cathy Hatcher, Jordan M. Winter, Carl J. Vaughan, Mairead Casey, Jie He, Cathy Hatcher, Jordan M. Winter, Stanislawa Weremowicz, Kate Montgomery, Raju Kucherlapati, Cynthia C. Morton, and Craig T. Basson, Department of Cardiology, Division of Medicine, University of Louisville, KY

Cardiac myxomas arise from primitive pluripotent mesenchymal cells within the subendocardium. In autosomal dominant Carney complex, intramyocardiac deformed architecture is seen. We previously localized the Carney complex gene defect to chromosome 17q23-q24, which is deleted in these patients. We now demonstrate that mutations in the chromosome 17 PKR1α gene encoding the R1α regulatory subunit of cAMP-dependent protein kinase A (PKA) cause inherited cardiac myxomas and Carney complex. We detect heterozygous deletions in the PKR1α gene in three unrelated kindreds (JFster/Gy088 in Family YA, JFster/L9253 in Family YB, JFster/Th163 in Family YF). These mutations were confirmed by bidirectional sequence analysis and by denaturing acrylamide gel electrophoresis. Each mutant produces a frameshift premature termination codon with consequent truncation. DNA and protein analysis of an atrial myxoma resected from a resected individual in Family YA reveals that the tumors retain both the wildtype and mutant PKR1α alleles, and that wildtype R1α but not mutant protein is stably expressed. However, western blot analysis demonstrates a reversal of the ratio of PKA regulatory subunits R1α to R1β in the myxomas that can alter PKA activity and contribute to tumor development. Our data, then suggest, that PKR1α acts as a tumor suppressor gene in the heart via regulation of PKA activity. These novel findings implicate the cAMP-dependent PKA signaling pathway as a critical modulator of cardiac cell growth and differentiation. This involvement of PKA in the heart may ultimately foster new therapeutic strategies for cardiac cell regeneration.

Functional Proteomic Analysis of Protein Kinase C ε Signaling Complexes in Preconditioning.

Peipei Ping, Jun Zhang, Roberto Boll, Cardiology Division, University of Louisville, KY

Studies from our laboratory and others have shown that transgenic (tg) mice expressing low levels of active protein kinase C ε (PKC-ε) exhibit resistance to ischemic injury, a cardioprotected phenotype analogous to that observed during preconditioning. Although PKC-ε has been shown to activate multiple downstream targets in preconditiosing, the molecular components that activate PKC-ε signaling complex during this state of cardioprotection are unknown. We used a proteomic approach to characterize PKC-ε signaling complexes. PKC-ε monomeric antibodies were used to immunoprecipitate cardiac tissues from PKC-ε tg mice and wild type mice (n=10 each). Combining 2-D electrophoresis, MALDI mass spectrometry, and immunoblotting, so far we have identified 27 known and 12 unknown molecules in PKC-ε signaling complexes. These include signaling proteins (RACK1, Lck, Src, Pck2, Pkca, p170/65), p38 MAPK, p54/p46 JNKS, Erk1a, Heh27/71, v-8ustinbl, anios, eNOS, and structural proteins (cardiac α-actin, tropinin T, α-tropomyosin, prohibitin, desmin, Lap, caveolin-3). Many of these proteins were not previously suspected to be in PKC-ε immuno-complexes. In PKC-ε tg mice, altered expression and post-translational modification were evident in 27 known and 12 unknown proteins. These data, when compared to wild type mice, may provide clues to the role of PKC-ε in cardiac disease.

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

Tatsoba S, Bowles KR, Vatta M, Zintz C, Bowles NE, Towbin JA, Pediatric Cardiology, Baylor College of Medicine, Houston, TX

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 sporadically occurring. The majority of familial DCM occurs as an autosomal dominant trait. Mutations in the δ-sarcoglycan (δ-sarcoglycan) gene were screened for mutations using single strand conformation polymorphism (SSCP), denaturing high performance liquid chromatography (DHPLC) and DNA sequencing. Protein structural analysis and immunohistochemistry were performed.

Results: Mutation analysis of the DCM pedigree identified a single nucleotide change in exon 6 of δ-sarcoglycan causing an amino acid change from a polar (serine) to nonpolar amino acid (alanine) altering the protein secondary structure. In 2 of the 5 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 δ-sarcoglycan staining. Conclusions: Mutation of the δ-sarcoglycan gene causes autosomal dominant DCM. As mutations of this gene are also known to cause the Syrian hamster cardiomyopathy 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 DCM pedigrees.

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

Wei-Zhong Zhu, Ming Zheng, Brian Kobikia*, Rui-Ping Xiao, Laboratory of Cardiovacular Science, GRC, MA, NIH, Baltimore, N4D 21224;*Howard Hughes Medical Institute, Stanford Univ Med Cent, Stanford, CA 94305.

Cardiac β2-AR activates both Gi 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 crossstalks between β-AR subtypes, we express β1-AR or β2-AR individually in the null background. β1-2 double knockout mutants are null for both β1-AR and β2-AR. Using adult mouse myocyte culture 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 β1-2AR 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-coupled receptor, we first examined the possible involvement of p38 MAPK, since recent studies suggest that p38 MAPK underlies Gi-dependent anti-apoptotic effects. We found that although stimulation of either β1-AR subtype increases p38 MAPK activity, this effect is insensitive to PTX, excluding 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 Gi protein, or blocking β3-adrenoceptor. So the differently effects of β-AR subtypes on cardiac cell survival and apoptosis may have important pathophysiological and therapeutic implications in chronic heart failure.
TARGET: Do Tirofiban And ReoPro Give Similar Efficacy Trial? 
Eric J. Topol et al

_Circulation_. 2000;102:2672
doi: 10.1161/01.CIR.102.21.2672-1
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2000 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/102/21/2672.8

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/