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cytoskeleton reorganization and cell shape changes in terms of lamellipodia formation in KO VSMCs compared with WT VSMCs.
Conclusions: These findings suggest that CHF1/Hey2 is an important regulator of VSMC motility during vascular remodeling through control of PDGF and HB-EGF dependent signaling pathways.

Noon

406-5 **Oxidized Low-Density Lipoprotein-Stimulated Smooth Muscle Cell Growth Is Mediated by the Helix Loop Helix Factor Id3: A Novel Mechanism Contributing to Atherosclerotic Lesion Formation**

Angela M. Taylor, Feng Li, Ross Gerrity, Richard L. Birnbaum, Martin Matsumura, Sarah Rutherford, Puspha-Rekha Thimmalapura, Coleen A. McNamara, University of Virginia, Charlottesville, VA

Background: Oxidation of LDL has emerged as the initiating event in cardiovascular lesion formation. Little is known about the molecular mechanisms linking Ox-LDL and vascular smooth muscle cell accumulation, the harbinger of vascular lesion progression. The HLH transcription factor Id3 is a redox sensitive gene that is expressed in VSMC in response to mitogen stimulation and vascular injury. Id3 is a regulator of growth and differentiation in several other cell types. Accordingly we hypothesize that Id3 is an important mediator of Ox-LDL-induced VSMC growth.
Methods: Primary vascular smooth muscle cells were infected with AdId3 or AdGFP control and assayed for cell number, BrdU incorporation and $p21^{cip1}$ expression by Western blot analysis. Parallel cultures were stimulated with Ox-LDL or nLDL or sera from hyperlipemic, atherosclerotic pigs or normolipemic pigs without vascular lesions.
Results: Results demonstrated that increasing Id3 expression in VSMC decreased $p21^{cip1}$ expression and increased BrdU incorporation and cell number. Cotransfection with pAdId3 and $p21^{cip1}$ promoter-luciferase reporter construct demonstrated that Id3 regulates $p21^{cip1}$ promoter activation in VSMC. Ox-LDL and hyperlipemic porcine sera increase Id3 protein expression and VSMC proliferation. Consistent with the role of Id3 as an inhibitor of $p21^{cip1}$ expression, infection with pAdId3 increased BrdU incorporation and increased cell number. Stimulation with hyperlipemic sera increased cell number and S-phase entry. Furthermore, aortas of hyperlipemic pigs demonstrated significantly more Id3 than normolipemic controls.
Conclusion: The HLH factor Id3 mediates the mitogenic effect of hyperlipemic sera and Ox-LDL in VSMC via inhibition of $p21^{cip1}$ expression and inhibition of DNA synthesis. Moreover, hyperlipemic, atherosclerotic animals express greater amounts of Id3 protein in the vessel wall than normolipemic controls providing the first in vivo evidence implicating Id3 as an important mediator of atherogeneis.

YOUNG INVESTIGATOR AWARDS

408

Young Investigators Awards Competition: Clinical Investigations-Cardiology & Cardiovascular Surgery

Monday, March 08, 2004, 2:00 p.m.-3:15 p.m.
Morial Convention Center, Room 257

2:00 p.m.

408-1 **Genetic Polymorphism G894T on Endothelial Nitric Oxide Synthase Gene as a Risk Factor for Premature, Nonfatal Myocardial Infarction in Young Male Smokers**

Charalambos Antoniades, Dimitris Tousoulis, Christos Pitsavos, Carmen Vasiliadou, Christina Chrysochoou, Marina Toutouza, Demosthenis Panagiotakos, Costas Tentolouris, Pavlos Toutouzas, Christodoulos Stefanadis, Athens University Medical School, Cardiology Department, Hippokration Hospital, Athens, Greece

Background. Endothelial nitric oxide synthase (eNOS) gene polymorphism G894T has been associated with arterial hypertension and myocardial infarction (MI) in older ages. However, its role in the pathogenesis of premature MI remains unclear. We investigated whether this polymorphism is associated with premature non-fatal MI.
Methods. This case-control study enrolled 212 young patients with premature non-fatal MI (aged 46.5±5.2 years old) and 577 healthy age- matched controls (aged 48.1±13.5 years old), derived from ATTICA cohort. Polymerase chain reaction was done to detect G894T polymorphism on the eNOS gene. X^2 was used to test the significance of an association between eNOS genotype and the presence of premature MI (under the age of 50).
Results. Homozygosity for the 894T allele, existed in 27 MI patients (13%) and in 58 (10.1%) controls (p=0.281). The frequency of T allele was 0.552 among cases and 0.518 among controls (p= 0.126). In comparison to 894G homozygotes, the odds ratio for MI was 1.406(95%CI: 0.843 to 2.347, p= 0.191) for 894T homozygotes and 1.172 (95%CI: 0.837 to 1.64, p=0.355) for heterozygotes respectively. However, among male smokers, homozygosity for this polymorphism was observed in 23 of 179 MI cases (12.8%) and only in 7 of 157 controls (4.5%) (p=0.008). Among male smokers, the odds ratio for MI in TT homozygotes was 3.367 (95%CI: 1.369 to 8.279, p= 0.006) compared to GG, 2.935 (95%CI: 1.184-7.277, p=0.017) compared to GT and 3.159 (95%CI:1.317-7.581, p=0.007) compared to GG+GT. However, no association between G894T polymorphism and premature MI was observed in male non-smokers and in female smokers or non-smokers.
Conclusions. The present study supports that G894T polymorphism on eNOS gene may interact with smoking leading to premature, non-fatal myocardial infarction in young males.

2:15 p.m.

408-2 **Cardiac Troponin Elevations in Marathon Runners: Prevalence and Risk Factors**

Elizabeth B. Fortescue, Andrew Y. Shin, David S. Greenes, Rebekah Mannix, Nader Rifai, Michael J. Landzberg, Jane W. Newburger, Christopher SD Almond, Children's Hospital Boston, Boston, MA, Harvard Medical School, Boston, MA

Background: Elevations in serum cardiac troponins have been found to occur in runners completing long distances.Our objectives were to determine prevalence of and risk factors for troponin elevations in marathon finishers.
Methods: Entrants in the 2002 Boston Marathon were recruited the weekend prior to the race, at which time we obtained demographic, health history, and training data. At race completion, we obtained race performance data and serum third-generation troponin T (cTnT) and I (cTnI) levels. Potential risk factors for troponin elevations were selected a priori from clinical suspicion and literature review and were evaluated using logistic regression analysis.
Results: A total of 482 runners completed surveys and had labs drawn. In all, 33% were female, 20% were aged <30 years, and 92% had run at least one prior marathon. Compared to males, females were significantly younger (p<0.001), slower (p<0.001), and less experienced marathoners (p=0.018). The majority of marathon runners in our cohort (68%) had some degree of troponin elevation after completing the marathon (cTnT$\geq$0.01 ng/mL or cTnI$\geq$0.1 ng/mL); of these, 55 (17%) had significant elevations (cTnT $\geq$0.075 ng/mL or cTnI$\geq$0.5 ng/mL). On multivariate analysis, individuals at greatest risk of significant troponin elevations were less experienced marathoners (<5 prior marathons run, O.R. 3.3, 95% C.I. 1.6-6.6, p<0.001) and younger runners (<30 years, O.R. 2.4, 95% C.I. 1.3-4.5 p=0.006). Female gender was a univariate but not multivariate correlate, and health history, anthropometrics, family history, training intensity, and race performance were not associated. Young age and marathon inexperience were robust predictors of troponin elevations over a broad range of threshold values analyzed and with troponins evaluated as continuous variables.
Conclusion: In a large and athletically diverse group of marathon finishers, we found that significant troponin elevations were common, and that less experienced marathoners and younger runners were at greatest risk of experiencing elevations. Further prospective research by our group into potential clinical significance of these findings is ongoing.

2:30 p.m.

408-3 **Quantitative Detection of Inflammation in Carotid Atherosclerosis by Dynamic Contrast Enhanced Magnetic Resonance Imaging**

William S. Kerwin, Marina Ferguson, Kevin O'Brien, Thomas Hatsukami, Chun Yuan, University of Washington, Seattle, WA

Background: Inflammation in advanced atherosclerotic plaque is a primary catalyst for disruption of the plaque and subsequent thromboembolic events. Thus, a quantitative, non-invasive technique for characterizing inflammation would be invaluable for detecting vulnerable, inflamed plaques and monitoring therapeutic response. We hypothesize that the dynamic response of magnetic resonance imaging (MRI) to an injected gadolinium contrast agent can be used for quantitative evaluation of inflammation by measuring the transfer constant K^{trans} between the blood plasma and the extracellular space. This parameter is derived from the curve of enhancement vs. time and quantifies the increased vascularity, permeability, and extracellular water content associated with the inflammatory response.
Methods: The association of K^{trans} with macrophages, the predominant inflammatory cells in human carotid atherosclerotic plaque, was evaluated in 18 carotid endarterectomy patients. Within one week prior to surgery, cross-sectional MRI scans centered at the carotid bifurcation of each patient were performed using a dynamic protocol (fast spoiled gradient echo; 15 seconds per image; 10 time frames), which included injection of 0.1 mmol/kg of a standard, low molecular weight gadolinium contrast agent. Kinetic modelling of the MRI results was used to estimate K^{trans} and the fractional plasma volume v_p of the plaque. After surgery, the endarterectomy specimens were sectioned, matched to the MRI results, and double-stained for macrophages (HAM56) and vascular endothelial cells (Ulex, to mask cross-labelling by HAM56). The relative area of each specimen staining positive for macrophages was measured and normalized by the total plaque area.
Results: Macrophage content of the excised specimens was found to correlate strongly with K^{trans} (R= 0.74, p=0.0005) as measured by MRI.
Conclusion: K^{trans} serves as a powerful marker of inflammation for clinical evaluation of atherosclerotic plaque. The strong correlation suggests it can be used to measure therapeutic response aimed at reducing plaque inflammation.