model, highlighting this receptor's potential role in the prevention of restenosis in the diabetic patients..

Table. Morphometric Data

	Zucker fat rats		Zucker lean rats	
	Placebo (n=12)	Treatment (n=8)	Placebo (n=10)	Treatment (n=7)
Luminal area (mm^2)	0.15±0.05	0.22±0.06*	0.21±0.04	0.23±0.04
Neointimal Area (IA, mm^2)	0.21±0.05	0.15±0.05*	0.14±0.06	0.12±0.03
Medial Area (MA, mm^2)	0.10±0.01	0.10±0.01	0.11±0.03	0.10±0.01
External Elastic Lamina (mm^2)	0.45±0.05	0.47±0.05	0.46±0.05	0.44±0.04
IA/MA	2.10±0.47	1.43±0.47*	1.21±0.41	1.21±0.30

* P< 0.05 when compared with placebo.

9:45 a.m.

808-3 **Vascular Injury Induces Expression of Periostin: A Novel Vascular Extracellular Matrix Protein via the PI3-Kinase-MAP Kinase Pathway**

Guohong Li, David Wang, Yiu-Fai Chen, Suzanne Oparil, University of Alabama at Birmingham, Birmingham, AL

Periostin (PN, also known as osteoblast-specific factor-2, OSF2), is a novel cell adhesion protein secreted by osteoblasts and osteoblast-like cell lines that has been described in the embryonic heart but not in adult cardiovascular tissues. Based on previous findings from our laboratory and others that extracellular matrix (ECM) proteins such as osteopontin (OPN) play an important role in vascular remodeling following endoluminal injury, we tested the hypotheses that PN is expressed in arteries in the setting of acute vascular injury and explored the signaling mechanisms involved using rat aortic smooth muscle cells (RASMCs) in vitro. Sprague Dawley rats (male, 10-wk old) were subjected to balloon injury of the right carotid artery and sacrificed at 3 days (n=7) and 7 days (n=6) post injury. Uninjured right carotid arteries from sham-operated rats were used as controls (n = 6). PN and OPN mRNA expression was analyzed by Northern blot. PN and OPN mRNA were undetectable in uninjured control vessels but increased post injury, with a peak at 3 days. PN mRNA expression in cultured RASMCs was robustly stimulated by growth factors (10 ng/ml of FGF-1, PDGF-BB) and angiotensin II (100 nM), (2.5-, 2-, and 3.2- fold increases), respectively. This stimulatory effect was completely inhibited by pretreatment with either the PI3 kinase inhibitor (LY294002, 10 uM) or the MAP kinase inhibitor (U0126, 5 uM). In contrast, OPN mRNA expression was not affected by LY294002 and only partially (50%) inhibited by U0126. This study provides a first demonstration that vascular injury induces PN expression, likely via the PI3-kinase- MAP kinase pathway, suggesting a contribution of this novel ECM protein to neointima formation following vascular injury.

10:00 a.m.

808-4 **Systemic Markers of Inflammation Do Not Predict Coronary In-Stent Restenosis in Stable Angina Patients Treated With HMG CoA Reductase Inhibitors**

Abuzeid Gomma, Gideon Hirschfield, June Gallimore, Gordon Lowe, Mark Pepys, Kim Fox, National Heart and Lung Institute and Royal Brompton Hospital, London, United Kingdom, Royal Free and University College Medical School, London, United Kingdom

Introduction: C-reactive protein (CRP), serum amyloid A protein (SAA), and interleukin-6 (IL-6), can predict coronary restenosis following angioplasty and stent deployment. In view of the anti-inflammatory activity of HMG CoA reductase inhibitors (statins), we reviewed this association in statin treated stable angina patients, undergoing angioplasty and stenting. **Methods:** We investigated this association in 182 stable angina patients, in whom 152 underwent elective coronary artery stenting and a further 30, diagnostic angiography alone. Of the patients as a whole, 80% were receiving HMG CoA reductase inhibitors. At 6 months 133 stented patients were restudied and the target lesions quantified. Baseline and serial CRP, SAA and IL-6 values were measured by high sensitivity immunoassays; values are reported as medians. **Results:** The binary restenosis rate at follow-up was 33.8%. There were no significant differences in values of CRP, SAA or IL-6 between patients with or without in-stent restenosis. Patients with pre-procedural values of CRP, SAA or IL-6 greater than the median, continued to have elevated values at follow up.Pre-procedural values of CRP and SAA did not differ between patients undergoing angiography alone or angioplasty plus stenting (CRP: 3.7mg/l vs 3mg/l; SAA: 4.1mg/l vs 3.5mg/l), despite a small difference in values of IL-6 (1.92pg/ml vs 2.78pg/ml, P=0.02). Pre-procedural values of CRP, but not SAA or IL-6, correlated positively with BMI (P=0.01). Higher values of CRP (5.95 mg/l vs 2.95mg/l, P=0.09) and SAA (4.9mg/l vs 3mg/l, P=0.026) were seen in women, while smokers or ex-smokers had elevated values of CRP (3.85mg/l vs 2.15mg/l, P<0.001). **Conclusion:** Pre- or peri-procedural values of CRP, SAA or IL-6, are not associated with coronary in-stent restenosis in stable angina patients in contrast to previous report in patients predominantly with unstable angina. In addition to differences in pathobiology between stable and unstable coronary syndromes, the widespread use of statins with anti-inflammatory activity, reflected by suppression of CRP production, may mask the association.

10:15 a.m.

808-5 **Obligate Role of Macrophage Colony-Stimulating Factor for the Development of Neointimal Thickening Following Arterial Injury**

Tripathi B. Rajavashisth, Ming Liu, Hiroyuki Tanaka, Jagannath Tripathi, Pinky Tripathi, Arthur Loussararian, Peter Libby, Hiroyasu Uzui, Aatish Kumar, Terence M. Doherty, Bojan Cercek, Sanjay Kaul, Prediman K. Shah, Cedars-Sinai Medical Center, Los Angeles, CA, Brigham & Women's Hospital and Harvard Medical School, Boston, MA

Although evidence suggests that macrophage-colony stimulating factor (M-CSF) participates critically in atherosclerosis, little is known about the role of M-CSF in the development of neointimal hyperplasia following mechanical vascular injury. We examined the expression of M-CSF and its receptor, *c-fms*, in rodent and rabbit models of arterial injury. Injured rat carotid arteries expressed 3- to 10-fold higher levels of M-CSF and *c-fms* mRNA within 24 hours following balloon injury as compared to uninjured arteries. The levels of mRNA paralleled the expression of immunoreactive M-CSF and *c-fms* protein. In the rabbit, M-CSF protein expression was greatest in neointimal smooth muscle cells (SMCs) post injury, with some expression also observed in medial SMCs. M-CSF-positive neointimal and medial SMCs exhibited markers of proliferation. At 30 days post injury, neointimal SMCs in the adjacent healed area near the border between injured and uninjured zone lost both proliferative activity and overexpression of M-CSF. The presence of induced M-CSF and *c-fms* expression correlated with the initiation of SMCs proliferation. We, therefore, investigated *in vitro* the effect of exogenous M-CSF on the proliferation of cultured human aortic SMCs (HASMCs). Recombinant human M-CSF stimulated an increase in the incorporation of [^{3}H] thymidine in HASMCs in a concentration-dependent manner, and this effect was inhibited by a rat monoclonal antibody specific to the cell surface epitope of human *c-fms*. The presence of *c-fms* transcript and protein in HASMCs was demonstrated by Northern and Western blot analysis, respectively. To test further the role of M-CSF in vivo, we induced arterial injury by placing a periadventitial cuff around the carotid arteries in compound mutant mice lacking apolipoprotein (apo) E and M-CSF. Homozygous loss of M-CSF (the *op* mutation) abolished the neointimal hyperplastic response to arterial injury in apo E knockout mice. Local delivery of M-CSF to the injured artery restored neointimal proliferation. Taken together, our experimental studies suggest a critical role for M-CSF signaling through *c-fms* for neointimal thickening in response to arterial injury.

ORAL CONTRIBUTIONS

813 Predictors of Restenosis After Stent Placement

Monday, March 31, 2003, 11:00 a.m.-12:15 p.m.
McCormick Place, Room S401

11:00 a.m.

813-1 **Elevated Baseline C-Reactive Protein is Associated With Increased Risk of Death and Myocardial Infarction at One Year Following Percutaneous Coronary Intervention**

Joel P. Reginelli, David S. Lee, Derek P. Chew, Ivan P. Casserly, Kent Dauterman, Kent W. Dauterman, Stephen G. Ellis, The Cleveland Clinic Foundation, Cleveland, OH

Background: An elevated baseline C-reactive protein (CRP) prior to PCI has been associated with worse outcomes at 30 days; however, the longer term prognostic significance of an elevated value is not well established. We sought to determine if an elevated baseline CRP prior to PCI impacts long-term outcomes at 1-year. **Methods:** Using a single-center interventional registry database, we identified 1644 consecutive PCI patients in whom baseline pre-procedural CRP values were prospectively collected. Patients were divided into 4 quartiles (Q) based on CRP value (in mg/dl): Q1<0.16, Q2=0.16-0.40, Q3=0.41-1.10, and Q4>1.10. One year outcome data, including death and MI, were collected on all patients. **Results:** For each increasing quartile of CRP, there was a significantly increased risk of death (Figure) and death/MI at one year (death-X^2=66, p<0.0001; death/MI-X^2=43, p<0.0001). Using a Cox proportional hazards model to adjust for confounding by age, lesion score, LVEF, ACS, renal insufficiency, BMI, and statin therapy, baseline CRP remains a significant predictor of 1-year death or MI (HR=1.24 [CI=1.08-