

Arteriosclerosis, Thrombosis, and Vascular Biology

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Brief Reviews

Molecular Mechanisms of Vascular Calcification: Lessons Learned From The Aorta

Jian-Su Shao, Jun Cai, Dwight A. Towler 1423

Vascular calcification increasingly afflicts our aging and dysmetabolic population. Once considered a passive process, it has emerged as an actively regulated form of calcified tissue metabolism, resembling the mineralization of endochondral and membranous bone. In this review, we discuss the biology of vascular calcification. We highlight how aortic fibrofatty tissue expansion (adventitia, valve interstitium), the adventitial-medial vasa, vascular matrix, and matrix vesicle metabolism contribute to the regulation of aortic calcium deposition, with greatest emphasis placed on diabetic vascular disease.

The Multiple Languages of Endothelial Cell-to-Cell Communication—ATVB In Focus

Stefan Liebner, Ugo Cavallaro, Elisabetta Dejana 1431

Excess NO causes apoptosis through the ER stress pathway in some types of cells. It was found that the ER stress pathway is activated by various stresses, and when stresses are severe, apoptosis is induced. The NO-induced ER stress pathway may be involved in pathogenesis of various vascular diseases.

Nitric Oxide and Endoplasmic Reticulum Stress—ATVB In Focus

Tomomi Gotoh, Masataka Mori 1439

Excess NO causes apoptosis through the ER stress pathway in some types of cells. It was found that the ER stress pathway is activated by various stresses, and when stresses are severe, apoptosis is induced. The NO-induced ER stress pathway may be involved in pathogenesis of various vascular diseases.

T Cell Costimulation in the Development of Cardiac Allograft Vasculopathy: Potential Targets for Therapeutic Interventions

Mitsuaki Isobe, Hisanori Kosuge, Jun-ichi Suzuki 1447

Cardiac allograft vasculopathy (CAV) is a serious complication after heart transplantation. Continuous minor endothelial cell damage and subsequent T cell activation evoke inflammatory processes. Many costimulatory pathways for T cell activation are involved. The role of these pathways in CAV development and atherogenesis are discussed in this brief review.

Vascular Biology

New Insights to Vascular Smooth Muscle Cell and Pericyte Differentiation of Mouse Embryonic Stem Cells In Vitro

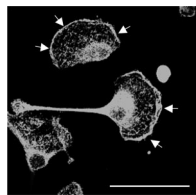
Henrik Lindskog, Elisabet Athley . . . Per Lindahl 1457



We developed an ES cell-based angiogenesis/vasculogenesis model and characterized the system for VSMC and pericyte differentiation. Five days of culture on OP9 feeder cells induced expression of VSMC/pericyte-specific genes in mouse ES cells. The induction was temporally separated from the induction of SMC-specific genes, which suggest regulation by separate mechanisms. Finally, PDGFB and TGF β 1 were dispensable for pericyte differentiation.

Combination of In Vivo Angiopoietin-1 Gene Transfer and Autologous Bone Marrow Cell Implantation for Functional Therapeutic Angiogenesis

Koichi Kobayashi, Takahisa Kondo . . . Toyooki Murohara 1465



Ang-1 gene and BM-MNCs combination therapy significantly augmented the angiographic score and capillary density, accompanied by functional improvement of skin ulcer score and TcO_2 in the ischemic limb. This new Ang-1 gene and BM-MNC combination therapy enhances not only quantitative but also qualitative angiogenesis in ischemic tissues.

Comparative Effects of Paclitaxel and Rapamycin on Smooth Muscle Migration and Survival: Role of Akt-Dependent Signaling

Cam Patterson, Sabeen Mapera . . . Peter Charles 1473

We used smooth muscle cells to compare the activities of rapamycin and paclitaxel. Rapamycin potently activates AKT-dependent signaling, an effect that causes phosphorylation of FOXO1. This effect is associated with attenuation of the anti-migratory effects of rapamycin and with protection against cytotoxicity, both of which are dependent on FOXO1 phosphorylation.

Protection of Endothelial Survival by Peroxisome Proliferator-Activated Receptor- δ Mediated 14-3-3 Upregulation

Jun-Yang Liou, Sang Lee . . . Kenneth K. Wu 1481

We postulated that EC-synthesized PGI_2 protects ECs from apoptosis. Results show that PGI_2 generated by transduction with an adenoviral vector containing a bicistronic cyclooxygenase-1 and PGI_2 synthase construct (Ad-COPI) or synthetic carbaprostacyclin (c PGI_2) suppressed H_2O_2 -induced EC apoptosis by a novel PPAR δ -mediated 14-3-3 ϵ transcriptional upregulation.

Dimethylarginine Dimethylaminohydrolase 2 Increases Vascular Endothelial Growth Factor Expression Through Sp1 Transcription Factor in Endothelial Cells

Kazuhiro Hasegawa, Shu Wakino . . . Koichi Hayashi 1488

This study demonstrates PKA- and Sp1-dependent transcriptional upregulation of VEGF by DDAH2 in vascular endothelial cells. This mechanism is specific for DDAH2 and independent of NO/NOS system. The induction of VEGF by DDAH2 may contribute to DDAH-induced angiogenesis and constitute a novel therapeutic target of angiogenesis-related diseases.

Evidence for a Functional Role of Endothelial Transient Receptor Potential V4 in Shear Stress-Induced Vasodilatation

Ralf Köhler, Willm-Thomas Heyken . . . Joachim Hoyer 1495

Ca^{2+} -permeable mechanosensitive channels are believed to be important in endothelial mechanotransduction. The present study provides evidence that the TRPV4 channel, a putatively mechanosensitive member of the TRPV family, mediates wall shear stress-induced vasodilatation in a NO-dependent manner.

Matrix Metalloproteinase 2 Activation of Transforming Growth Factor- β 1 (TGF- β 1) and TGF- β 1-Type II Receptor Signaling Within the Aged Arterial Wall

Mingyi Wang, Di Zhao . . . Edward G. Lakatta 1503

We analyzed MMP-2 effects on TGF- β 1 activation status and downstream signaling during age-associated arterial remodeling. MMP-2 increased TGF- β 1 activity, collagen, and fibronectin within aortic rings or VSMCs from young rats to the levels that occur in old animals. All of these effects are substantially reduced by inhibition of MMP-2.

Matrix Metalloproteinase Inhibition Attenuates Aortic Calcification

Xiao Qin, Matthew A. Corriere . . . Raul J. Guzman 1510

Arterial calcification is associated with MMP-mediated matrix degradation. Inhibiting MMP activity with doxycycline or the synthetic MMP-inhibitor GM6001 prevents calcium accumulation in the arterial wall.

Cardiomyocyte-Specific Overexpression of NO Synthase-3 Protects Against Myocardial Ischemia-Reperfusion Injury

John W. Elrod, James J.M. Greer . . . David J. Lefler 1517

Cardiomyocyte-specific eNOS overexpression (CS eNOS-Tg) versus systemic overexpression (SYS eNOS-Tg) was evaluated in MI-R injury. CS eNOS-Tg mice displayed decreased infarct size and preservation of cardiac function compared with SYS eNOS-Tg mice. These results provide evidence that site-specific targeting of eNOS gene therapy may be more advantageous in limiting MI-R injury.

Estrogen Receptor β Protects the Murine Heart Against Left Ventricular Hypertrophy

Fawzi A. Babiker, Daniel Lips . . . Pieter A. Doevendans 1524

E2 protects the murine heart against LVH via ER β . Presence of E2 antagonizes the increase in heart weight with TAC. This protective effect is played by blocking the increased phosphorylation of p38-MAPK and increasing the expression of ANF. ER α appears to be involved in regulation of other processes.

Therapeutic Potential of a Synthetic Peptide Inhibitor of Nuclear Factor of Activated T Cells as Antirestenotic Agent

Haixiang Yu, Karen Sliedregt-Bol . . . Erik A.L. Biessen 1531

Synthetic peptide inhibitor of NFAT selectively and potently inhibits NFAT activation and vSMC proliferation. NFAT and MEK–ERK pathways act in concert to trigger vSMC proliferation. NFAT is the key regulator essential for PDGF-BB–induced vSMC proliferation. VIVIT peptide may lead to more selective and less toxic approaches in antirestenosis therapy.

Atherosclerosis and Lipoproteins

Elevated Plasma Active Matrix Metalloproteinase-9 Level Is Associated With Coronary Artery In-Stent Restenosis

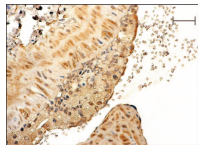
Gregory T. Jones, I. Patrick Kay . . . M.J.A. Williams **Web Site Feature** @e121–e125

Abstract 1538

This study aimed to determine whether plasma MMP-9 or TIMP-1 levels were elevated in patients with a history of (bare metal) in-stent restenosis. Plasma active MMP-9 was independently associated with ISR with a stratified risk association with the number of sites of ISR. Future studies should therefore prospectively evaluate plasma levels of active MMP-9 as a possible independent predictor of ISR.

Atheroprotective Effects of Neuronal Nitric Oxide Synthase in Apolipoprotein E Knockout Mice

Peter J. Kuhlencordt, Stefanie Hötten . . . Georg Ertl 1539



Here we test whether neuronal NOS (nNOS) deficiency affects atherosclerosis in apoE/nNOS α double knockout (DKO) and apoE knockout animals. Male and female DKO animals showed a significant increase in lesion-area. Thus, nNOS α protects against atherosclerosis. Female but not male DKO mice showed a significant reduction in mean arterial blood pressure.

Human Paraoxonase-1 Overexpression Inhibits Atherosclerosis in a Mouse Model of Metabolic Syndrome

Bharti Mackness, Rozenn Quarck . . . Paul Holvoet 1545

We used adenovirus-mediated PON1 gene transfer to overexpress human PON1 in mice with combined leptin and LDL receptor deficiency, a model of metabolic syndrome. Overexpressing PON1 in this mouse model of metabolic syndrome inhibited the development of atherosclerosis, probably by reducing oxidized LDL in the plaque and plasma, thereby preventing its proatherogenic effects.

Involvement of the Antimicrobial Peptide LL-37 in Human Atherosclerosis

Kristina Edfeldt, Birgitta Agerberth . . . Zhong-qun Yan 1551

To understand the function of vascular innate immunity in atherosclerosis, we investigated the role of the antimicrobial cathelicidin peptide LL-37 in atherosclerosis. We found that LL-37 is produced in atherosclerotic lesions, where it may function as an immune modulator by activating adhesion molecule and chemokine expression, thus enhancing innate immunity in atherosclerosis.

Oxidized Low-Density Lipoprotein Correlates Positively With Toll-Like Receptor 2 and Interferon Regulatory Factor-1 and Inversely With Superoxide Dismutase-1 Expression: Studies in Hypercholesterolemic Swine and THP-1 Cells

Paul Holvoet, Penelope C. Davey . . . Gérard Marguerie 1558

We searched for genes of which their expression in macrophages correlates with the complexity and oxidized LDL content of plaques in coronary arteries of hypercholesterolemic swine. Among 1653 deregulated genes, the interferon regulatory factor 1 (IRF1; $R^2=0.69$) and toll-like receptor 2 (TLR2; $R^2=0.18$) were the strongest positive gene correlates of both complexity and oxidized LDL content. Superoxide dismutase 1 (SOD1; $R^2=0.57$) was the strongest inverse correlate of oxLDL. IRF1 and TLR2 protein correlated positively, and SOD1 protein correlated negatively with plaque oxLDL. OxLDL-induced THP-1 foam cell generation was associated with increased IRF1 and TLR2 and decreased SOD1 expression.

Adipocyte Differentiation-Related Protein Promotes Fatty Acid Storage in Cytosolic Triglycerides and Inhibits Secretion of Very Low-Density Lipoproteins

Björn Magnusson, Lennart Asp . . . Sven-Olof Olofsson 1566

An increase in the amount of ADRP sequestered fatty acids in triglycerides in cytosolic lipid droplets and prevented them from being incorporated into triglycerides of VLDL. A knockdown (siRNA) decreased the pool of cytosolic lipid droplets and promoted the β -oxidation of the stored fatty acids and the secretion of apoB-48 VLDL1.

Atheroprotective Potential of Macrophage-Derived Phospholipid Transfer Protein in Low-Density Lipoprotein Receptor-Deficient Mice Is Overcome by Apolipoprotein AI Overexpression

David T. Valenta, Nicolas Ogier . . . Catherine M. Desrumaux 1572

Using bone marrow transplantation, macrophage-derived PLTP was shown to be atheroprotective in hypercholesterolemic mice fed a high-fat diet. This effect was only observed in mice with normal apoAI plasma levels and not in transgenic mice with elevated human apoAI plasma levels.

Secretory Phospholipase A₂ Group V: Lesion Distribution, Activation by Arterial Proteoglycans, and Induction in Aorta by a Western Diet

Birgitta Rosengren, Helena Peilot . . . Eva Hurt-Camejo 1579

sPLA₂-V was observed in human and mouse lesions associated with smooth muscle cells and surrounding foam cells in lipid cores. Proteoglycans increased the activity of sPLA₂-V toward low-density lipoproteins. Western diet induced sPLA₂-V expression in mouse aorta but not that of sPLA₂-IIA. These enzymes may contribute to atherosclerosis by different pathways.

Lipoprotein-Associated Phospholipase A₂ Predicts Future Cardiovascular Events in Patients With Coronary Heart Disease Independently of Traditional Risk Factors, Markers of Inflammation, Renal Function, and Hemodynamic Stress

Wolfgang Koenig, Dorothee Twardella . . . Dietrich Rothenbacher 1586

We found that lipoprotein-associated phospholipase A₂ (Lp-PLA₂) strongly predicts secondary cardiovascular events in patients with manifest coronary heart disease (CHD). In multivariable analysis, even including markers of inflammation, renal function, and hemodynamic stress, patients in the top tertile of the Lp-PLA₂ mass and activity distribution showed ≈2-fold increased risk compared with those in the bottom tertile.

Intrinsic Fluorescence and Diffuse Reflectance Spectroscopy Identify Superficial Foam Cells in Coronary Plaques Prone to Erosion

George O. Angheloiu, Joseph T. Arendt . . . Michael S. Feld 1594

We demonstrate that intrinsic fluorescence and diffuse reflectance accurately detect coronary plaques with superficial foam cells associated with proteoglycans and smooth muscle cells, 2 markers of coronary erosion. This is a step in our program to develop spectroscopic techniques for real-time in vivo diagnosis of vulnerable atherosclerotic plaque.

Identifying Inflamed Carotid Plaques Using In Vivo USPIO-Enhanced MR Imaging to Label Plaque Macrophages

Rikin A. Trivedi, Chinthake Mallawarachi . . . Jonathan H. Gillard 1601

The in vivo detection of plaque inflammation was evaluated using a macrophage labeling MRI contrast agent. Areas of focal signal loss on MRI corresponded to macrophage populations, thereby identifying inflamed plaques in 24 of 27 symptomatic individuals with severe ICA stenosis were detected and confirmed histologically.

Coronary Atherosclerosis and Alcohol Consumption: Angiographic and Mortality Data

Romana Femia, Andrea Natali . . . Ele Ferrannini 1607

In 2141 consecutive patients undergoing quantitative coronary angiography for the clinical work-up of ischemia, moderate (<231 g/wk in men, <154 g/wk in women) alcohol consumption was associated with less coronary atherosclerosis and a lower risk (HR, 0.84; 95% CI, 0.71 to 1.00) of cardiac death at follow-up independently of classical cardiovascular risk factors.

Gene Variants of VAMP8 and HNRPUL1 Are Associated With Early-Onset Myocardial Infarction

Dov Shiffman, Charles M. Rowland . . . James J. Devlin 1613

Genetic associations with early-onset myocardial infarction were identified by testing successively fewer SNPs in 3 consecutive case-control studies. Thus, 11 647 SNPs were tested in the first study, 666 in the second study, and only 8 SNPs were tested in the third study.

Identification of a Novel C5L2 Variant (S323I) in a French Canadian Family With Familial Combined Hyperlipemia

Michel Marcil, Hai Vu . . . Katherine Cianflone 1619

DNA sequencing of C5L2-ASP receptor identified a heterozygous Ser323→Ile substitution in the carboxyl-terminal region. Eight heterozygous family members demonstrated increased plasma triglyceride, cholesterol, LDL, apolipoprotein B and ASP. C5L2(+/-) cells had reduced ASP response and B_{max}. S323I may alter C5L2 function and contribute to familial combined hyperlipidemia.

Thrombosis

Biologically Active CD40 Ligand Is Elevated in Sickle Cell Anemia: Potential Role for Platelet-Mediated Inflammation

Sheritha P. Lee, Kenneth I. Ataga . . . Leslie V. Parise 1626

CD40L is elevated in plasma but depleted from platelets in sickle cell anemia (SCA). These differences are exaggerated during painful crises. CD40L is implicated in SCA plasma-induced production of tissue factor, ICAM-1, and B cells, suggesting that platelet-derived CD40L contributes to inflammation and coagulation in SCA.

Local Heat Shock Priming Promotes Recanalization of Thromboembolized Microvasculature by Upregulation of Plasminogen Activators

Martin Rücker, Thilo Schäfer . . . Michael D. Menger 1632

Using a rat thromboembolization model and intravital fluorescence microscopy, this study demonstrates that heat shock priming induces endothelium-derived plasminogen activator expression *in vivo*, and accelerates spontaneous recanalization of thromboembolized microvasculature. This was completely blunted by application of plasminogen activator inhibitor-1. Thus, heat shock induces endogenous hyperfibrinolysis, which promotes recanalization of thromboembolized microvasculature.

Two-Phase Antithrombotic Protection After Anti-Glycoprotein VI Treatment in Mice

Valerie Schulte, H. Peter Reusch . . . Bernhard Nieswandt 1640

Collagen and thrombin are major platelet agonists. The collagen receptor GPVI is an attractive antithrombotic target because its inhibition/absence results in profound antithrombotic protection but no bleeding in mice. We show that mice treated with the anti-GPVI antibody JAQ1 transiently display reduced platelet responses to thrombin and protection against lethal tissue factor-induced thromboembolism.

Clopidogrel Improves Systemic Endothelial Nitric Oxide Bioavailability in Patients With Coronary Artery Disease: Evidence for Antioxidant and Antiinflammatory Effects

Thomas Heitzer, Volker Rudolph . . . Stephan Baldus 1648

Platelet adenosine phosphate receptor blockade by clopidogrel improved endothelium-dependent vasodilation to acetylcholine and vascular bioavailability of nitric oxide in the human forearm of patients with symptomatic coronary artery disease. In addition, inflammatory parameters, ie, hsCRP, sCD40L, and RANTES and oxidative parameters, ie, 8-iso-PG F_{2α} were reduced. These findings support the concept that activated platelets contribute to endothelial dysfunction and impaired nitric oxide bioavailability.

Fibrin and Activated Platelets Cooperatively Guide Stem Cells to a Vascular Injury and Promote Differentiation Towards an Endothelial Cell Phenotype

H.C. de Boer, C. Verseyden . . . A.J. van Zonneveld 1653

The hemostatic factors fibrin and activated platelets cooperatively provide the local cues for CD34⁺ cells to escape (tether and roll) from flowing blood, migrate towards an injury, and differentiate into a more mature endothelial phenotype, ultimately leading to repair of a vascular injury.

Less Effect of Intranasal Than Oral Hormone Therapy on Factors Associated With Venous Thrombosis Risk in Healthy Postmenopausal Women

Majoie Hemelaar, Jan Rosing . . . Marius J. van der Mooren 1660

This randomized, double-blind clinical trial in 90 healthy postmenopausal women compared the effects of intranasal E₂/NET and oral E₂/NETA therapy on nAPCsr and on other hemostatic parameters associated with venous thrombosis. Effects in the intranasal group were smaller than in the oral group, which may suggest a lower venous thrombosis risk.

Soluble CD40L Levels Are Regulated by the -3459 A>G Polymorphism and Predict Myocardial Infarction and the Efficacy of Antithrombotic Treatment in Non-ST Elevation Acute Coronary Syndrome

Anders Mälarstig, Bertil Lindahl . . . Agneta Siegbahn 1667

Elevation of soluble CD40L was associated with myocardial infarction in the FRISC-II trial, which enrolled 2457 patients with acute coronary syndromes. A prolonged dalteparin treatment was more beneficial in patients with elevated sCD40L. The -3459 A>G SNP in the CD40LG gene was identified as a novel regulator of sCD40L levels.

Dietary Factors Related to Higher Plasma Fibrinogen Levels of Japanese-Americans in Hawaii Compared With Japanese in Japan

Katsuyuki Miura, Hideaki Nakagawa . . . Jeremiah Stamler 1674

We investigated whether dietary factors explain higher plasma fibrinogen levels in Japanese emigrants living a Western lifestyle in Hawaii compared with Japanese in Japan. Data from this epidemiologic study indicate that higher intakes of iron, sugar, and caffeine, plus obesity, account largely for higher fibrinogen levels with Westernized lifestyle.