Targeting Vimentin Receptors for Noninvasive Radionuclide Imaging of Atherosclerosis

Dagmar Hartung, Anton Petrov, Frank Kolognit, Naumet Narula, Scott D. Edwards, Nezam Heider, Renu Virmani, Jagat Narula, Drexel University College of Medicine, Philadelphia, PA, Armed Forces Institute of Pathology, Washington, DC

Background: Vimentin receptor plays a pivotal role in smooth muscle cell (SMC) migration in vascular injury, neointimal proliferation during plaque development and progression, and post-angioplasty restenosis. We investigated the feasibility of targeting vimentin receptor for noninvasive imaging of experimentally induced atherosclerotic lesions.

Methods: A radio labeled 3 integrin antagonist (111-In-RP 748, Bristol-Myers Squibb) was utilized for imaging in 6 NZW rabbits with experimentally induced atherosclerotic lesions and in 7 unmanipulated control rabbits. Atherosclerosis was induced by abdominal aorta denudation followed by a cholesterol rich diet (1%-5% peanut oil) for 12 weeks. Control rabbits were fed normal chow for 12 weeks. Gamma images were obtained after 2hr and 111-In-RP 748 administration.

Results: Atherosclerotic lesions were clearly visible in all six rabbits. Quantitative 111-In- RP 748 uptake in atherosclerotic lesions was 5 times higher than the background activity in the corresponding regions of the control rabbits (mean percent injected dose per gram, 0.07±0.01 versus 0.01±0.004; P<0.05). Correlation between histophotometric indices of SMC proliferation, macrophage proliferation, and radioguide uptake was performed.

Conclusion: Noninvasive imaging of experimentally induced atherosclerotic lesions using 111-In-RP 748 is feasible and may be useful for early detection of SMC proliferation such as post-angioplasty restenosis.

Increased To-99m-Annexin Uptake in Doxorubicin Induced Myocardial Apoptosis

Dobrochnis S. Gospodarz, Dagmar Hartung, Anton Petrov, Naumet Narula, Vindurupa Patel, Zheng Liu, Mani A. Vannan, Jagat Narula, Drexel University School of Medicine, Philadelphia, PA

Background: Doxorubicin (Dox) treatment is limited by irreversible cardiomyopathy; apoptosis may contribute to myocardial damage. Simultaneously, induction of apoptosis in the malignant tissue is necessary for oncology. Since phosphatidylserine is exposed on the outer cell surface during apoptosis, Annexin V has a high affinity for membrane bound phosphatidylserine, we used To-99m-labeled Annexin V (TAN) imaging to study acute and chronic Dox induced myocardial apoptosis in rats.

Methods: Eight male Sprague Dawley rats weighing 250-300 g were injected with Dox, group 1: acute, group 2: chronic. Group 1: 0.1 mg/kg, i.p. (acute group. n=4). Four control animals were included in each group and treated with saline. Both groups were imaged using TAN at the end of 2 and 5 weeks respectively. Gamma imaging was performed after i.v. injection of 1.0-2.1 mCi of TAN. Hearts were excised and sliced into four segments and percent injected dose per gram (%) ID) of Annexin V uptake was measured. Myocardial specimens were submitted for histopathologic examination and TUNEL and caspase-3 staining.

Results: On ex vivo imaging, Dox toxicity analysis showed increased activity in their hearts as compared to their respective controls. The highest uptake was visualized in group2. 1% ID TAN uptake was 0.98 ± 0.14 % in group 2 and 0.88 ± 0.26 % in group 1 which were significantly higher than corresponding controls (0.43 ± 0.15 % and 0.32 ± 0.05 % respectively; p<0.001). Basal myocardial segments in both groups showed highest increase in TAN.

Conclusion: Doxorubicin induces myocardial apoptosis in rats and it should be possible to image myocardial damage and remission of tumor mass simultaneously by TAN.

Mechanism of Sustained Retention and Clearance From Myocardium and Other Organs

Bhindi Joseph, Kuldip K. Bhargava, Jihlender Kandiallai, Harmeet Malhi, Michael Schisky, Christopher J. Palestro, Dwijkar Jain, Sanjeev Gupta, Long Island Jewish Medical Center, Long Island, NY, Drexel University College of Medicine, Philadelphia, PA

Background: To-99m-sestamibi (MIBI), is widely used for myocardial perfusion imaging. Following its administration, MIBI has stable myocardial retention whereas it clears from all other organs. The exact mechanism of its selective retention in the myocardium is not clear.

Methods: Hepatic clearance of MIBI after intrasplenic injection by serial imaging was studied in following groups of animals: inbred wild-type FVB/N normal mice (n=5), knock-out FVB/N mice with specific P-glycoprotein deficiency (n=10), normal Long Evans Agouti (LEA) rats (n=4) and mutant Long Evans cinnamon (LEC) rats (n=4) with liver dissection following copper toxicosis but intact P-glycoprotein expression.

Results: After intrasplenic injection, MIBI rapidly Incorporated in the liver of normal mice and rats within 30 min. Maximal accumulation at 120 min was 10%\(\pm\)1 and 10%\(\pm\)1.6% respectively (p<0.05). In normal mice and rats, 55±11% and 55±6%, respectively, of maximal MIBI activity was retained in the liver at 1 hr. In mice lacking both homologs of the single human multi-drug resistance gene 1, mdr1a and mdr1b genes (double knockout mice, n=6), 88±11% of maximal MIBI activity was retained in the liver at 1 hr; (p<0.001). In single knockout mice, mdr1a was deficient in either mdr1a (n=5) or mdr2 gene (homolog of MDR2 gene in humans) (n=7), hepatic MIBI excretion was also impaired (p<0.05). Hepatic MIBI excretion was unchanged in E.C.T. rats despite significant liver disease compared to the normal rats.

Conclusion: MIBI is a substrate for MDR1 and MDR3 gene products. These genes are abundantly expressed in other liver organs but not expressed in the heart. A lack of MDR gene expression in the normal myocardium explains a relative lack of myocardial clearance of MIBI. Inactivation of MDR gene results in marked impairment of hepatic MIBI clearance. Other MDR substrates may also have potential for use as myocardial perfusion imaging agents.

Ischemic Stroke Causes Regional Denervation in Rat Myocardium

Avraham A. Krillobsky, Dong-wei Gao, Alexander Kopelnik, Nilita Derugin, Michael Wendland, William O'Donnell, Jonathan G. Zaroff, Michael W. Dae, UCSF Medical Center, San Francisco, CA

Background: ECG changes, troponin release and reduced left ventricular ejection fraction (LVEF) in the presence of a critical coronary stenosis. However, during CVT stress, TL tracked flow better than MIBI, and produced larger SPECT defects.

Conclusion: This study provides unique evidence that myocardial denervation occurs after CNS injury, strongly supporting the theory that this form of cardiac dysfunction is neurally mediated.

Persistent Myocardial Sympathetic Denervation in Patients With Neurogenic Injury

Alexander Kopelnik, Poyee P. Tung, Nader M. Banki, Michael W. Dae, Michael T. Lawson, Daryl Green, Barbara J. Drew, Elias Fourrier, William W. Parmeley, Jonathan G. Zaroff, UCSF, San Francisco, CA

Introduction: ECG changes, troponin release and reduced left ventricular ejection fraction (LVEF) in the presence of a critical coronary stenosis. However, during CVT stress, TL tracked flow better than MIBI, and produced larger SPECT defects.

Conclusion: This study provides unique evidence that myocardial denervation occurs after CNS injury, strongly supporting the theory that this form of cardiac dysfunction is neurally mediated.