Towards Dual-Mode Imaging of Vulnerable Plaques

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Introduction

Heart disease is one of the leading killers in developed nations, in the United States alone there are over 5 million Americans suffering from cardiovascular diseases and over a third of all deaths are due to cardiac disease. Clinically, angiography is used to image plaque impingement on the vessel lumen (stenosis). However, the more critical contributor to acute coronary syndromes is plaque rupture. It is now understood that certain plaque compositions, such as high macrophage content, are correlated with vulnerability to rupture. But angiography provides no information about plaque composition, only stenosis; therefore a need exists for a method to assess plaque stability/composition in vivo. We describe a novel nanoparticle probe for dual-mode magnetic resonance (MRI) and positron emission tomography (PET) imaging of vulnerable plaques.

Methods

We have developed a nanoparticle based probe to assess macrophage content of plaques. This agent contains MRI and PET detectable tracers coupled to ligands targeted to macrophage specific scavenger receptors. The nanoparticle agent is an iron oxide particle coated with the ligand dextran sulfate and conjugated to chelators (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) bearing a positron emitter $^{64}Cu^{2+}$. Dextran sulfate coated particles (ADIO) were synthesized by doping a small amount of dextran sulfate into a dextran solution in the presence of iron chloride salts. Nanoparticle structure was characterized by transmission electron microscopy and dynamic light scattering, and magnetic properties by NMR relaxivity. To determine cellular uptake, murine macrophages were incubated with ADIO particles and dextran coated particles for comparison and MR signal intensity was measured. Additionally, macrophages were incubated with ADIO and dextran sulfate, a known macrophage scavenger receptor (SRA) ligand, to determine if uptake was receptor mediated and iron uptake was determined by Atomic Absorption Spectroscopy. Rat and mouse models of atherosclerotic disease were injected with agent by tailvein and imaged by MRI and PET.

Results

The agent was successfully synthesized as verified by transmission electron microscopy, dynamic light scattering, and nuclear magnetic resonance relaxivity. Significant uptake of the probe was demonstrated by macrophages in culture. Dual mode imaging of animal models of atherosclerotic plaque were performed and demonstrate signal enhancement in experimentally generated plaques. Image below left shows T1 weighted FLASH image of carotid arteries in coronal view, the artery on the right has been injured and images show the thicker vessel walls of the injured artery. Image on right shows overlay of PET and MR showing correlation of PET signal with the injured vessel.

Conclusions

The results here serve as a foundation for developing methods to image markers of plaque instability *in vivo*. The ultimate goal is to assess plaque composition *in vivo* first using the sensitivity of PET to identify putative lesions, and then focusing on the lesions with high resolution MRI for determination of plaque macrophage content.