Biology and Pathology

Cardiovascular Disease

Introduction to Molecular Contrast Agents and New Devices – Atherosclerosis

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Learning Objectives:

- Describe the role of molecular imaging in diagnosis and therapy of atherosclerosis
- Describe target-specific contrast agents for key processes in plaque formation, destabilization and rupture

Many mechanisms are known to play a role in the development of atherosclerosis and the associated thrombotic clinical events. These insights have led to significant improvements in disease outcome, as exemplified by the development of statin therapy. Nevertheless, cardiovascular disorders remain a prime cause of death worldwide. Conventional anatomic imaging techniques (such as X-ray ontrast angiography for assessing arterial stenosis and MRI for visualizing plaque dimensions) have limited utility in atherosclerosis diagnostics, as lesions that do not cause a flow-limiting stenosis are the main cause of fatal myocardial infarctions. Thus, there is a pressing need for imaging methodologies that go beyond stenosis visualization and are capable of informing specifically on cellular and molecular processes that govern atherosclerotic lesion development. In recent years, molecular imaging has emerged as a powerful tool to assess biological aspects of atherosclerotic plaques that are not captured by anatomical imaging (for excellent recent reviews see Refs. 1 and 2). This educational lecture highlights the basics of molecular and cellular imaging as applied in the setting of atherosclerosis research, the key requirements in terms of contrast agents, as well as the relative strengths of the major imaging methods that are used in this field.

Molecular and cellular imaging of atherosclerosis exploit all major imaging modalities [2] i.e. X-ray CT, PET, SPECT, MRI, optical imaging and contrast-enhanced ultrasound, each presenting inherent strengths and weaknesses. The nature, location and abundance of the molecular and cellular targets to a large ex tent determine the types of contrast agent as well as the imaging modalities that are most effective. As an example, the activation of endothelial cells lining arteries is associated with an increased expression of adhesion molecules, such as VCAM-1 and ICAM-1, which are involved in the initiation of local inflammation and therefore are considered important targets of atherosclerosis molecular imaging. Ligands for targeting these factors include peptides and antibodies. All major imaging modalities have been used to probe adhesion molecule up-regulation in atherosclerosis. Nanoparticle contrast agents have proven very effective [3], as they are largely restricted to the blood pool such that there is little background signal from contrast material that has permeated (non-target) tissue beyond the vasculature. Another benefit of nanoparticles is they carry a high payload of contrast material, thus enabling the visualization of low levels of target expression. A third virtue of nanoparticles is that they are also well suited as drug carrier devices for theranostic approaches [1]. Nanoparticle contrast agents that have been successfully used include iron oxides for MRI, lipid-based materials such as liposomes and micelles for MRI and nuclear imaging, as well as micro-bubbles for contrast-enhanced ultrasound. Several examples of other contrast agent-imaging modality combinations will be given to illustrate their use for the detection of key features of atherosclerotic lesions, including the presence of inflammatory

cells, metabolic activity, cell death, oxidative stress, extracellular matrix components and thrombus formation.

References:

1. Quillard T, Libby P. Molecular imaging of atherosclerosis for improving diagnostic and therapeutic development Circ Res 111: 231-244, 2012
2. Leuschner F. Nahrendorf M. Molecular imaging of coronary atherosclerosis and myocardial infarction: considerations for the bench and perspectives for the clinic. Circ Res 108: 593-606, 2011
3. Mulder WJ, Strijkers GJ, van Tilborg GA, Cormode DP. Fayad ZA. Nicolay K. Nanoparticulate assemblies of amphiphiles and diagnostically active materials for multimodality imaging. Ace Chem Res 42: 904-914, 2009