Atherosclerosis is characterized by the thickening of the arterial wall to form an atherosclerotic plaque, a process in which cholesterol deposition, inflammation, extracellular-matrix formation and thrombosis have important roles (Sanz, 2008 #1). Symptoms occur late in the course of disease and are usually caused by the narrowing of the lumen of the artery, which can happen gradually (as a result of progressive plaque growth) or suddenly (as a result of plaque rupture and, subsequently, thrombosis). The resultant decrease in blood supply can affect almost any organ, although coronary heart disease and stroke are the most common consequences.

Traditionally, diagnosis of atherosclerosis was possible only at advanced stages of disease, either by directly revealing the narrowing of the arterial lumen (stenosis) or by evaluating the effect of arterial stenosis on organ perfusion. However, new imaging approaches allow the assessment not only of the morphology of blood vessels but also of the composition of the vessel walls, enabling atherosclerosis-associated abnormalities in the arteries (including the coronary arteries) to be observed, down to the cellular and molecular level in some cases. Some of these approaches are now in clinical use or are being tested in clinical trials, whereas others are better suited to basic and translational research.

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Molecular imaging relies on the use of contrast agents that target specific cells or molecular pathways of relevance to disease. In addition to the various imaging techniques being developed, contrast agents for tracking potentially important components of atherosclerotic disease are at various stages of development (see Table 1 in Sanz, 2008). Most of the available probes are in experimental testing, although some have already advanced to clinical evaluation. Imaging probes typically include a moiety (such as an antibody or specific ligand) with high affinity for the desired target molecule. Alternatively, the probe can be modified to facilitate uptake by specific cells. In addition, probes are designed to be detected by various modalities, including ultrasound (which detects microbubbles), SPECT and PET (radioactive isotopes), MRI (paramagnetic and superparamagnetic compounds), CT (iodinated compounds) or optical imaging (fluorochromes). Many of the targets of interest are located in deep organs and are present at very low (nanomolar) concentrations; imaging modalities therefore need to be highly sensitive, as well as safe and economically viable.

Ultrasound is widely available, safe and inexpensive, but it has insufficient penetration for the non-invasive imaging of deep vessels (including the coronary arteries) with high spatial resolution or sensitivity. SPECT and PET have a high sensitivity, but they also have limited spatial resolution and the additional disadvantage of requiring the use of radioactive agents. By contrast, MRI has a somewhat lower sensitivity than SPECT and PET and requires prolonged imaging times, but it is safe and provides excellent resolution (~10 µm with high-field magnets). CT, conversely, offers the advantages of fast scanning times and superior performance for coronary angiography, at the expense of limited sensitivity and the use of nephrotoxic agents and ionizing radiation. Optical imaging techniques — for example, near-infrared fluorescence reflectance or fluorescence molecular tomography — have excellent sensitivity and temporal resolution and allow the tissue distribution of the probe to be precisely determined with ex vivo fluorescence microscopy. So far, however, such techniques can be used non-invasively only to monitor superficial structures because of the limited ability of light to penetrate tissue. Optical imaging techniques and some SPECT and MRI techniques have the advantage of being able to detect more than one molecular signature at a time.
appealing targets. Ultrasmall paramagnetic iron-oxide particles are engulfed by macrophages in vivo, and this causes a detectable decrease in the MRI signal in proportion to the degree of atherosclerotic plaque inflammation, as shown in human studies (Trivedi, 2006 #2). The use of dynamic contrast-enhanced MRI using Gd has been shown to yield important compositional information about the plaque such as neovessels distribution (Calcagno, 2008 #12). A strong correlation between macrophage density and MRI signal was also found recently in a mouse model of atherosclerosis, by using a contrast agent consisting of Gd\textsuperscript{3+}-loaded micelles targeted to the macrophage scavenger receptor (Amirbekian, 2007 #3). A recent study showed also the potential of this same technique to image with MR oxidized LDL in the plaques (Briley-Saebo, 2008 #4). Using biomimicry and lipoproteins such as high-density lipoprotein (HDL), a multimodal molecular imaging probe for macrophages has been demonstrated to be very flexible (Cormode, 2008 #6; Cormode, 2008 #7). Similarly, in rabbits, specific uptake of an iodine-containing contrast agent by macrophages allows atherosclerotic lesions to be detected by using CT (Hyafil, 2007 #5). Also, with PET, the signal from [18F]fluorodeoxyglucose correlates with the concentration of macrophages in human atherosclerotic plaques (Tawakol, 2006 #8). Moreover, by using specialized equipment, several imaging techniques can be used concurrently — for example, PET together with CT or, recently, MRI (Izquierdo-Garcia, 2008 #9) — for the sensitive and reproducible detection of vascular inflammation (Rudd, 2008 #11; Rudd, 2007 #10). This combination approach allows the most appropriate technique(s) for a particular patient, vascular region and/or disease stage to be chosen and takes advantage of the particular strengths of each modality. At the other end of the timeline of atherosclerotic-plaque progression, cell-adhesion molecules participate in the early development of lesions by facilitating the recruitment of leukocytes into the vessel wall. In an animal model, increased amounts of vascular cell-adhesion molecule 1 (VCAM1) were found in aortic plaques by using a dual contrast agent detectable by both MR and optical imaging (Nahrendorf, 2006 #15). Another possibility is to use probes that emit a detectable signal only after they have been activated by the target. For example, in a recent study of an experimental model of atherosclerosis, a fluorescent probe activated by enzymatic degradation was used to reveal intraplaque protease activity with intravascular cathether and near-infrared fluorescence (Jaffer, 2008 #13).
rabbits were administered paramagnetic nanoparticles loaded with an antiangiogenic drug, resulting in a reduction in the extent of blood vessels in atherosclerotic plaques, as observed by non-invasive tracking with MRI. {Winter, 2006 #14}

References:


