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Molecular Imaging of Vulnerable Plaque

Takehiro Nakahara, MD, PhD,[*,†,‡] Jagat Narula, MD, PhD,[†] and H. William Strauss, MD[*,†]

Molecular imaging provides multiple imaging techniques to identify characteristics of vulnerable plaque including I) Inflammatory cells (the presence and metabolic activity of macrophages), II) synthesis of lipid and fatty acid in the plaque, III) the presence of hypoxia in severely inflamed lesions, IV) expression of factors stimulating angiogenesis, V) expression of protease enzymes in the lesion, VI) development of microthrombi in late-phase lesions, VII) apoptosis, and VIII) microcalcification.

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Introduction

Rudolf Virchow, a 19th century pathologist, recognized atherosclerotic plaque as a product of inflammation. Since that description, a century of investigation has defined many of the molecular and cellular pathways that result in the evolution of an atheroma into vulnerable plaque, including monocyte mobilization, transformation of monocytes to phagocytic tissue macrophages at the site of the atheroma, toxic interaction of phagocytized lipids and cellular debris that result in the necrotic core, the structure of the atheroma (particularly the thin cap of atheroma) and the dual role of calcification (both in causing plaque rupture and in quenching the metabolic fire of the inflamed lesion[1] as well as the low likelihood of plaque rupture causing a clinical event). There are no specific circulating markers that specifically identify inflammation in atheroma, although nonspecific biomarkers of inflammation, such as C-reactive protein, can serve as a marker of risk for acute coronary events; however, the specificity of an elevated C-reactive protein is low.[1] The presence and density of vascular calcification in the coronary arteries on gated cardiac CT define the presence of coronary artery disease, but it does not identify specific lesions that are likely to cause a clinical event.[2] Invasive imaging with intravascular ultrasound and optical coherence tomography have shown that vulnerable plaques rupture and heal without causing a clinical event much more often than plaque ruptures causing clinical events.[3]

Because there is a range of inflammation in atheroma, it is clear that an imaging technique that can sample the entire vasculature is required to identify the lesions that are most likely to rupture. The first molecular imaging technique to study atheroma utilized ^{14}C and ^{3}H cholesterol administered to 13 patients[4] (either orally or intravenously or both) to determine the turnover of cholesterol in atheroma. Arterial specimens were obtained from 12 patients at carotid surgery and in one patient from multiple sites at autopsy. The cholesterol turnover time in the plaques was >400 days. In the 1980s in vivo images of the carotid arteries in three patients with known carotid artery disease and one control hyperlipidemic subject without carotid disease were described using autologous radioiodine-labeled low-density lipoprotein (LDL).[5-7] Subsequently, Tc-99m autologous LDL was utilized in 17 patients with atherosclerosis. In addition to imaging, carotid endarterectomy was performed on a subset of six patients. Ex vivo counting demonstrated 2- to 4-fold greater uptake in parts of the lesions with abundant foam cells and macrophages.[7]

In addition to imaging lipid and lipoprotein uptake in the vulnerable lesion, laboratory studies demonstrated the ability to detect increased expression of receptors for the chemotactic peptide MCP-1 (originally called monocyte chemoattractant peptide, recently renamed CXCR2)[8] at the site of atheroma.

Other approaches to detecting atheroma, such as detecting inflammation in the lesion with the glucose analog ^{18}F-fluorodeoxyglucose, was suggested by Vallabhajosula and Fuster in 1997.[9]

*Molecular Imaging and Therapy Service, Memorial Sloan Kettering Cancer Center, New York, NY.
†Division of Cardiology, Icahn School of Medicine at Mount Sinai, New York, NY.
‡Department of Diagnostic Radiology, Keio University School of Medicine, Tokyo, Japan.
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Address reprint requests to Takehiro Nakahara, MD, PhD, Molecular Imaging and Therapy Service, Memorial Sloan Kettering Cancer Center, New York, NY. E-mail: takehiro.nakahara@gmail.com

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In this article, we review the mechanisms of atherosclerotic plaque progression and tracers that can target specific steps in the evolution of vulnerable atheroma.

Mechanism of Plaque Progression

The adult intima is more than a single layer of endothelium, consisting of endothelial cells, smooth muscle cells, and collagen. The smooth muscle cells produce extracellular matrix, establishing an environment where "lipoprotein particles decorate the proteoglycans of the intima and coalesce into aggregates."[10] The lipoprotein proteoglycan complex is susceptible to oxidation, increasing the proinflammatory characteristics of the complex and stimulating a response to the inflammatory stimulus. Increased permeability of the multicellular endothelium allows the oxidized lipoprotein lipid to localize in the subintima, causing the expression of chemotactic peptides to attract leukocytes to phagocytize the offending oxidized lipoprotein. Circulating monocytes enter the lesion site to phagocytize the subendothelial irritant. Once in the tissue, the monocytes convert to tissue macrophages and commence the task of phagocytizing and catabolizing the lipoprotein cholesterol complex. In the process of catabolism, the phagocytized lipoproteins are further oxidized. The oxidized lipids are toxic to the macrophage, and once the macrophages have phagocytized a critical amount of lipoprotein, they initiate their programmed cell death process (apoptosis).[2] Although macrophages can change phenotype from M1, to Mox and M2, Mox and M2 is antioxidative and detoxifying,[11] the accumulation of oxidized LDL (ox-LDL) in M2 down regulate anti-inflammatory transcription factor (KLF2) and lead to a proinflammatory state.[11] T cells also play a role by producing antibodies that recognize ox-LDL, which accelerates the proinflammatory process.[2]

Depending on systemic conditions, such as hyperlipidemia and diabetes, the inflammation may persist or increase, resulting in attraction of more macrophages and an increase in the metabolic rate of macrophages in the lesion. Macrophages require exogenous glucose to produce adenosine triphosphate (ATP) for their cellular activities. Glycolysis requires oxygen; consumption of oxygen in the lesion makes the intraplaque environment hypoxic and acidotic. The low pO_2 in the lesion causes production of hypoxia-inducible factors (HIF-1), promoting the production of vascular endothelial growth factor (VEGF) to increase the flow of blood and oxygen to the lesion.[12] The microvessels produced in response to these stimuli originate from adventitia without supporting cells, causing these vessels to be very fragile. The fragile vessels are leaky, allowing intact erythrocytes (with their cholesterol-containing cell membranes) to enter the lesion, increasing the local cholesterol concentration, adding to the inflammatory stimuli. The fragile vessels can also rupture, causing intraplaque bleeding, which increases pressure within the lesion and causes rupture of the plaque cap.[13]

An additional contributor to inflammation is ineffective clearance of dead cells (primarily lipid-laden macrophages, but also smooth muscle cells and endothelial cells) in the lesion. Apoptotic cells are usually cleared from tissue by phagocytosis of the dead cell components by adjacent cells, a process called efferocytosis. When lipid-laden macrophages die, the cells begin to disintegrate. Delayed clearance of these dead cells allows the toxic intracellular contents to leak into the surrounding tissue, increasing inflammation and further decreasing the effectiveness of efferocytosis. The slow clearance of the remnants of apoptotic cells and the leak of toxic enzymes from the dead cells increase the size of the necrotic core.[14]

Components leaking from the dead cells include calcium and phosphate. In the absence of factors controlling the local concentration of these elements, and in the presence of extracellular vesicles released from macrophages and smooth muscle cells (serving as nucleation sites), microcrystals of calcium phosphate form.[15] The initial site of microcalcification is in the necrotic core. As microcalcification evolves to macrocalcification, the lesion is stabilized.[2] Macrocalcified plaque has a lower density of vasa vasorum[16] than microcalcified plaque (calcium phosphate particles <50 μm in diameter).[2] Microcalcification itself increases the risk of plaque rupture in ex vivo simulation models.[17]

Based on the evolution of atheroma, the following factors have become targets for vulnerable plaque imaging: I) Inflammatory cells (activated macrophages), II) lipid and fatty acid (LDL and ox-LDL), III) hypoxia, IV) angiogenesis, V) increased tissue concentration of proteases, VI) thrombosis, VII) apoptosis, and VIII) microcalcification. (Figure and Tables 1 and 2).

Targets and Tracers to Image Atheroma

I) Inflammatory Cells

I-a) Macrophage (membrane component, metabolism, receptor)

To deliver exogenous glucose to tissue macrophages, extracellular glucose is transported into the cell by the glucose transporters (GLUT 1 and GLUT 3) to produce ATP.[18,19] The glucose analog fluoro-deoxy-glucose (FDG) concentrates in regions of increased glucose utilization.[20] Inflamed atheroma and many neoplasms have increased glucose utilization. Glucose uptake is increased not only in macrophages but also in smooth muscle and endothelial cells in the lesion. The ability to quantify lesion uptake of FDG has led investigators to use serial vascular FDG imaging to determine the effectiveness of therapy.[21,22]

An alternative marker of macrophage activity measures incorporation of membrane lipid components ^{11}C-Choline or ^{18}F-Fluorocholine. These agents are phosphorylated by choline kinase, metabolized to phosphatidylcholine, and incorporated into the cell membrane. In activated macrophages (and tumor cells), choline or fluorocholine uptake in the lesion is increased. Laboratory studies in mice demonstrated a 2.3-fold increase in tracer uptake of ^{11}C-choline in plaques compared with healthy vessel.[23] A similar study in Apo $E^{-/-}$ mice demonstrated a 4.9-fold increase in ^{18}F-Fluorocholine localization in atheroma compared with normal vessel.[24]