Molecular imaging can be broadly defined as the in vivo characterization and measurement of biological processes at the cellular and molecular level. In this context, the noninvasive detection of molecular signatures of disease entities using molecular imaging holds great promise for the development of personalized medicine and drug development. One of the first clinically validated and useful tomographic molecular imaging techniques was implemented in the field of oncology, with the use of \( ^{18}\text{F} \) fluorodeoxyglucose (FDG) positron-emission tomography (PET) and, more recently, that of FDG PET/computed tomography (CT) in cancer diagnosis and management. Although traditionally the primary focus has been on cancer biology, molecular imaging techniques have been expanded into the field of cardiovascular disease for a wide variety of clinically important entities. Especially, the molecular imaging of atherosclerosis has gained much attention.

Several clinical imaging techniques have been applied for the purpose of molecular imaging of atherosclerosis, including ultrasound, CT, MRI, PET/CT, and single-photon emission computed tomography (SPECT)/CT. These imaging techniques are aimed at different targets of inflammation and vulnerability by using different targeting ligands. Because of their important role at all stages of atherosclerosis and plaque vulnerability, macrophages have been an important target for molecular images of atherosclerosis. A multitude of imaging approaches have been applied for this purpose, and more advanced in this respect is the assessment of metabolic activity (ie, glycolysis) in the vessel wall by using FDG-PET/CT and detection of macrophages with iron oxide nanoparticles. Other important targets within the vessel wall include apoptosis (targeting phosphatidylserine), the vascular cell adhesion molecules (targeting vascular cell adhesion molecule 1 and selectins), neovessels (targeting the integrin-\( \alpha\)v\( \beta\)3), oxidized low-density lipoproteins, thrombi, and protease activity of degrading enzymes (matrix metalloproteinases and cathepsins) within the atherosclerotic plaque.

The ability to detect an important target in the vessel wall implicated in atherosclerosis progression and, potentially, in vulnerability—the receptor of advanced glycation end products (RAGE)—has been missing to date. In this issue of Circulation: Cardiovascular Imaging, Tekabe et al demonstrate the noninvasive detection of RAGE in the atherosclerotic vessel wall of hypercholesterolemic mice. This is an exciting development that adds an important marker of atherosclerotic disease that can now be assessed noninvasively.

RAGE is a member of the immunoglobulin superfamily of cell-surface receptors. The ligand–RAGE axis has emerged as a central mechanism linked to vascular injury and atherosclerosis in diabetes and euglycemia. RAGE possesses a diverse range of ligands, and in the vessel wall, 3 are of particular importance: advanced glycation end products, S100/calgranulins, and high-mobility group box 1/amphoterin. In atherosclerosis, the ligands for RAGE are expressed in both diabetic and nondiabetic conditions, although to a higher degree in diabetes. RAGE itself is expressed in all cell types pertinent for the development and progression of atherosclerotic plaque (ie, endothelial cells, smooth muscle cells, monocytes/macrophages, and T and B lymphocytes). The interaction of RAGE ligands with RAGE in inflammatory cells and vascular cells leads to the activation of transcription factors, such as nuclear factor-kB, which leads to the upregulation of inflammatory cytokines, vascular adhesion molecules, matrix metalloproteinases, and tissue factor. Sustained activation of RAGE through its ligands leads to chronic cellular activation, promoting vascular inflammation and endothelial dysfunction, which ultimately lead to diabetic vascular complications and can augment atherosclerotic plaque development and progression at predilection sites.
Tekabe et al\textsuperscript{11} demonstrate, for the first time, the noninvasive specific detection of RAGE in the vessel wall. A nondiabetic atherosclerotic apolipoprotein E–deficient mouse model was used for this purpose, and a nuclear imaging technique was applied. A classical molecular imaging approach was chosen, with the creation of polyclonal antibodies against RAGE that were subsequently digested to F(\(ab\))\(_2\) fragments and conjugated to a \(\text{\^99mTc}\) radionuclide reporter. Validation was provided with fluorescent conjugated F(\(ab\))\(_2\) fragments and showed that the RAGE-conjugated probe localized mainly to macrophages but also endothelial cells and smooth muscle cells. This corresponds to the cell types staining positive for RAGE on histological sections and shows that the RAGE-specific probe was effective in reaching its target in the vessel wall.

Clearly, there are limitations to this study. First, a nontomographic imaging system with a low spatial resolution was used, therefore limiting detailed delineation of RAGE detection in the arterial wall. A tomographic micro-SPECT/CT system would have allowed a significantly better resolution. Another limitation is that polyclonal antibodies were used, which compared with monoclonal antibodies, have less specificity and higher background signal. Nevertheless, the study convincingly demonstrates the noninvasive detection of RAGE in the vessel wall of euglycemic atherosclerotic mice. Another important fact to consider is that RAGE promotes the expression of both matrix metalloproteinases and tissue factor, which both contribute to atherosclerotic plaque rupture and thrombosis. Therefore, the noninvasive detection of RAGE in the vessel wall could help define its role in plaque rupture, which has potentially important clinical implications. The study by Tekabe et al\textsuperscript{11} therefore represents significant progress in characterization of the biological role of RAGE.

In addition to its role in atherosclerosis and the development of vascular complication in diabetes, RAGE possesses wider implications in a variety of diseases, such as arthritis, cancer, liver disease, neurodegenerative disease, and sepsis, which underscores the importance of the ability of its noninvasive detection.\textsuperscript{13} Another exciting aspect is that, currently, specific RAGE inhibitors are being developed by the same group. Now having the ability to detect RAGE noninvasively, one can envision the noninvasive monitoring of treatment responses after application of RAGE inhibitors, at least in animal models, which will lead to the streamlined selection of potential drug candidates. In this context, high-affinity inhibitors can be functionalized with radionuclides and applied for imaging purposes as well as for validation of effective drug targeting.\textsuperscript{15}

The hope can now be that the biological role of RAGE can be studied noninvasively in vivo, which will clarify its role in many disease conditions and lead to better treatment of diabetic complications, atherosclerosis, and other diseases in which RAGE is implicated.

Disclosures
None.

References

\textbf{Key Words: arteriosclerosis \(\square\) imaging \(\square\) plaque \(\square\) radioisotopes}
"Feeling the RAGE" in the Atherosclerotic Vessel Wall
Zahi A. Fayad and Esad Vucic

doi: 10.1161/CIRCIMAGING.108.828152

Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/1/3/178

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Imaging can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Imaging is online at:
http://circimaging.ahajournals.org//subscriptions/