Intravascular Molecular Imaging for Atherosclerosis
– A Fledgling but Realistic World With Lights and Ultrasounds –

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Molecular imaging is now widely recognized in various domains of medicine. It is used to visualize, trace or characterize a specific molecular material and its physiological/pathological pathway within living organisms as well as human bodies. Regarding the use of this methodology, the clinical or research areas of atherosclerosis are not exceptional, because atherosclerosis comprises the dynamic movement of biological, chemical or pathological molecules. Many technical reports have used molecular imaging for clarifying the mechanism of atherosclerosis, especially in radiological medicine, including scintigraphy, magnetic resonance imaging and positron emission tomography. However, the principal activities of atherosclerosis occur in a more local and microscopic region within arterial vessels. The coronary artery is not large enough to observe the behavior of specific molecules using such imaging modalities in order to understand the mechanism or to prevent the catastrophe of atherosclerosis. To overcome these limitations, major areas of investigation into atherosclerosis are now focusing on how molecular imaging can be performed using modalities such as intravascular ultrasound (IVUS), optical coherence tomography (OCT), or coronary angioscopy, which have had great success in percutaneous coronary intervention and consequently led to an advanced maturity of the technology. Therefore, very recently, quite a few intravascular molecular imaging modalities have been proposed as research or clinical seeds in the field of atherosclerosis.

The main streams of development being attempted are as follows: (1) novel techniques of analyzing information obtained from conventional intravascular modalities; (2) specific agents for the enhancement of some imaging; (3) probes or labels for specific molecules, (4) new types of light or ultrasound used for emitting and receiving, (4) novel types of intravascular catheter; and (5) hybrid or combinations of multi-frequency lights, sounds, or light plus sound, and so on.

Table lists the variety of intravascular molecular imaging modalities. In the field of ultrasound imaging, contrast-enhanced representation is being considered. A new type of dual-frequency IVUS for detecting microbubbles was recently proposed for imaging vaso vasorum within arteries. The contrast agents were originally non-specific perfusion materials, but are currently more targeted with a coating linked to an antibody for a specific protein. Under these advancements, it has been proposed that IVUS can be used to detect molecularly targeted microbubbles in inflamed vasculature and subsequent gene or drug delivery.

The principles of intravascular optical imaging for molecules are shown in Figure. Conventional OCT with an axial resolution of 10 μm can identify calcification, fibrous and lipid constituents within atherosclerotic plaque (Figure A). In addition, OCT has been considered to be capable of detecting macrophage accumulation within coronary arteries. Beginning with this technology, a variety of intravascular “optical” imaging techniques for detecting specific molecules have been developed. Polarization-sensitive OCT detects collagen or smooth muscle cells by quantitating tissue-specific birefringence, which is related to the polarization of light (Figure B). Intravascular diffuse reflectance near-infrared spectroscopy (NIRS) identifies lipid-laden plaques by evaluating the absorbance of light at different wavelengths in the near-infrared spectrum (Figure C). NIRS is now commercially available with simultaneous IVUS imaging. Raman spectroscopy using Raman scatter, which has a different frequency to that of incident light (Figure D), can accurately detect biological or chemical molecules using such imaging modalities in order to understand the mechanism or to prevent the catastrophe of atherosclerosis.

Table. Techniques of Intravascular Molecular Imaging

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OCT, optical coherence tomography.

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Using an ultrasound detector, the sound waves can be detected and spatially resolved to provide an image of the optical absorption distribution in the tissue. This technique can also use nanoscale contrast agents or spectroscopic approaches to allow molecular imaging of atherosclerotic tissue. A contrary application idea has been proposed. Ultrasound-vibrated OCT elastography can measure tissue strain by ultrasound pressure, which might enable evaluation of the mechanical vulnerability of plaque.

In addition, various hybrid combination catheters for the abovementioned imaging modalities have been created. The ideas are generally good, but numerous hazards exist ahead, such as technological and patent issues, expensive safety and efficacy examinations, and approval difficulties by government. Especially, the development of very thin but less fragile optical fibers, or simultaneous concordant connections of 2 different physical media for communication between a rotating catheter and the console, is still a long way from successful application.

Among these attempts at intravascular molecular imaging, Uchida et al demonstrate in this issue of the Journal their unique dye-based method of coronary fluorescent angioscopy to identify native high-density lipoprotein (HDL) within the arterial wall using Fast green dye. They have so far suc-
ceeded in imaging localized crucial chemical components within atherosclerotic plaque, such as oxidized low-density lipoprotein, lysophosphatidylcholine, and ApoB-100. The technology is based on the principle of angioscopy using visible light, which represents a real color image of the plaque surface, whereas other techniques such as IVUS and OCT provide just a reconstructed image from depth-related characteristic values of physical tissue property with regards to light or ultrasound.

It is well accepted that the serum level of HDL is inversely related to the prevalence of coronary events, because of its protective role against the progression of atherosclerosis, including reverse transport of cholesterol from macrophages to the liver. However, the “native” level of HDL within the arterial wall is recently attracting the attention of investigators, because various local constituents within plaque have been reported to correlate with the serum HDL level. In the article by Uchida et al., they not only introduce a new attractive technology of their own, but also reveal the local distribution of HDL within the arterial wall, which apparently differs according to the stage of plaque progression. These findings contribute to our understanding of the process of atherosclerosis, and is a representative study showing a realistic, clinical feasibility of intravascular molecular imaging.

In conclusion, the world of intravascular molecular imaging is now fledgling, but becoming more and more mature and clinically feasible, which surely gives us great hope for advances in understanding and managing atherosclerotic disease.

Disclosures
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References