Oxidized Low-Density Lipoprotein and Atherogenesis

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Abstract

The development of atherosclerosis and ultimately obstructive coronary artery disease is a complex process. A critical step in this process is the oxidization of low-density lipoprotein (LDL) particles and their deposition in the arterial wall. These particles are particularly unstable. Current imaging techniques only allow one to note static views of atherosclerotic changes. Imaging of oxidized particles of LDL (OxLDL) through the use of antibodies directed against these particles has the potential of allowing clinicians to distinguish stable plaque from plaque that is more prone to rupture and result in arterial occlusion.

Keywords

Antibodies • Atherosclerosis • Lipoprotein • Oxidized • Imaging

Introduction

The association between oxidized low-density lipoproteins (oxLDL) and atherosclerotic coronary artery disease (ASCAD) enables oxLDL to serve as a potential biomarker for the early detection of ASCAD risk [1–4] and unstable plaque. Monitoring oxLDL levels can also provide evidence about the regression of ASCAD [5, 6]. The same properties that make oxLDL an attractive biomarker of ASCAD also make oxLDL a novel contrast agent for atherosclerotic imaging.

Several lines of evidence indicate the integral role played by LDL in atherosclerotic plaque formation:

- Early plaque formation relies heavily on the uptake and eventual oxidation of LDL particles [7, 8].
- Oxidized LDL has similar in vitro properties to LDL found in human atherosclerotic plaque [9].
- The LDL lipoprotein apo B-100 appears to be degraded during the oxidative process [7]. Products of this degradation are then expressed as new epitopes on the surface of the LDL particle. These new epitopes make the LDL particle susceptible to phagocytosis

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by macrophages, creating foam cells. Subendothelial deposition of foam cells forms the initial step in the production of fatty streaks within the coronary artery [7, 8]. Novel imaging techniques provide the ability to image early foam cell deposition [10].

Imaging Using Oxidized Low-Density Lipoproteins

- Imaging oxLDL would theoretically lead to the earlier clinical detection of unstable atherosclerotic plaque, an advantage over other techniques, such as cardiac CT static, which only detect more advanced forms of atherosclerosis.
- A repertoire of various antibodies whose epitope is the modified LDL particle have been isolated and/or generated from both animal and human sera [7, 9].
- An antibody against a malondialdehyde modified LDL particle (MDA) and another whose epitope is 4-hydroxynonenal conjugated LDL (4-HNE-LDL) were used to stain the atherosclerotic lesions of hyperlipidemic rabbits. These antibodies appear specific to modified forms of LDL in that they do not stain unmodified LDL [11].
- Radio-labeled antibodies, ^{125}I-MDA2, were first used to image the aorta of hyperlipidemic rabbits (Fig. 12.1).
- This same radio-labeled antibody has also been used in subsequent experiments to demonstrate the eventual regression of atherosclerotic plaque through a modified diet [12–14].
- Gamma camera scintigraphy of hyperlipidemic rabbits with ^{99m}Tc-MDA2 has also been used to successfully demonstrate areas of increased deposition of oxLDL [13] (Fig. 12.2).
- Radio-labeled (^{125}I) native, non-modified LDL in humans successfully imaged known carotid atherosclerotic disease in humans [15].
- Oxidized LDL was radio-labeled with ^{99m}Tc and used in patients who had recently suffered a transient ischemic attack. Carotid arteries with atherosclerotic plaque had significantly more uptake of the radio-labeled LDL than normal carotids [16].

Fig. 12.1 Sudan red stained aorta (*left*) of hyperlipidemic rabbit compared to radiograph of same after injection of 90 μCi ^{125}I-MDA2 (*right*) (Reproduced with kind permission of Springer Science + Businesss Media from Tsimikas et al. [19])

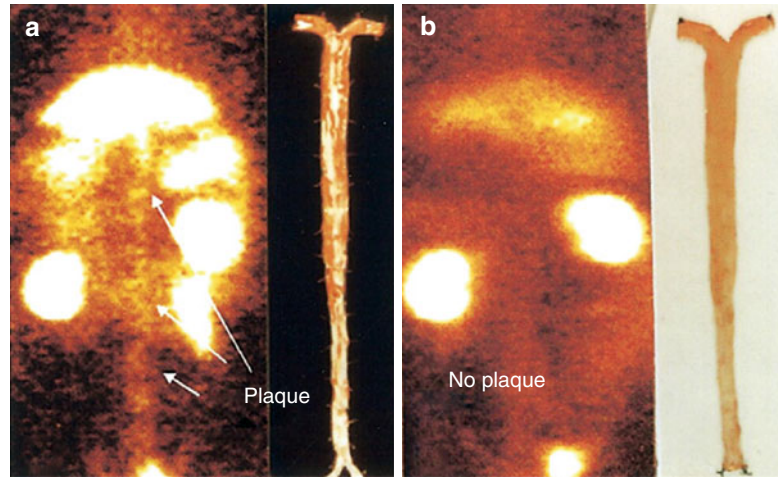

Fig. 12.2 (**a**, **b**) Scintigraphy with ^{99m}Tc-MDA2 with corresponding sudan red-stained aorta in hyperlipidemic rabbit (**a**) as compared to a normal rabbit (**b**) (Reproduced with permission of Elsevier from Tsimikas [13])

Future Directions

Native and oxLDL have successfully been labeled with fluorine-18. An obvious application of ^{18}F labeled oxLDL would be the assessment of plaque vulnerability in patients at risk for atherosclerosis by PET scanning [17]. To date, neither PET nor MRI [18] have been used for the imaging of oxLDL.

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