Review Article
Radiolabelled probes for imaging of atherosclerotic plaques

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Abstract: Cardiovascular disease is the leading cause of death worldwide. Unstable atherosclerotic plaques are prone to rupture followed by thrombus formation, vessel stenosis, and occlusion and frequently lead to acute myocardial infarction and brain infarction. As such, unstable plaques represent an important diagnostic target in clinical settings and the specific diagnosis of unstable plaques would enable preventive treatments for cardiovascular disease. To date, various imaging methods such as computed tomography (CT), magnetic resonance imaging (MRI), ultrasound (US), and intravascular ultrasound (IVUS) have been widely used clinically. Although these methods have advantages in terms of spatial resolution and the ability to make detailed identification of morphological alterations such as calcifications and vessel stenosis, these techniques require skill or expertise to discriminate plaque instability, which is essential for early diagnosis and treatment and can present difficulties for quantitative estimation. On the other hand, nuclear imaging techniques such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) can noninvasively collect quantitative information on the expression levels of functional molecules and metabolic activities in vivo and thus provide functional diagnoses of unstable plaques with high sensitivity. Specifically, unstable plaques are characterized by an abundance of invasive inflammatory cells (macrophages), increased oxidative stress that increases oxidized LDL and its receptor expressed on cells in the lesions, increased occurrence of apoptosis of macrophages and other cells involved in disease progression, increased protease expression and activity, and finally thrombus formation triggered by plaque rupture, which is the most important mechanism leading to the onset of infarctions and ischemic sudden death. Therefore, these characteristics can all be targets for molecular imaging by PET and SPECT. In this paper, we review the present state and future of radiolabelled probes that have been developed for detecting atherosclerotic unstable plaques with nuclear imaging techniques.

Keywords: Molecular imaging, atherosclerosis, plaque, positron emission tomography, single photon emission computed tomography, 2-[18F]Fluoro-2-deoxy-D-glucose, lectin-like oxidized low density lipoprotein receptor-1, apoptosis, matrix metalloproteinase, thrombus

Introduction
Despite recent therapeutic advances, cardiovascular disease remains the leading cause of death worldwide [1]. Since stenosis severity is reported to be a poor predictor of subsequent acute myocardial infarction (AMI) [1], methods to directly evaluate the biological properties of atherosclerotic lesions would be valuable diagnostic tools [2]. Atherosclerotic plaques formed by lipid accumulation in vessel lesions have a variety of characteristics, ranging from stable to unstable [3]. Unstable plaques are prone to rupture followed by thrombus formation, vessel stenosis, and occlusion and frequently lead to AMI and brain infarction [4, 5]. Thus, the specific diagnosis of unstable plaques would enable preventive treatments for AMI and brain infarction and represents a promising diagnostic target in clinical settings.

Unstable plaques are characterized by a large, soft lipid core that contains extracellular lipids and is covered by a thin fibrous cap, as well as an abundance of invasive inflammatory cells such as macrophages. In contrast, stable plaques have a small lipid core, thick fibrous caps, and little or no macrophage invasion with
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Figure 1. Atherosclerosis progression and potential targets for molecular imaging, MCP-1: monocyte chemotactic protein-1, LDL: low density lipoprotein, Mφ: macrophage, LOX-1: lectin-like oxidized LDL receptor-1, MMP: matrix metalloproteinase, MT-MMP: membrane type MMP, TF: tissue factor.

the development of fibrous tissue resulting in intimal thickening of the vessel [6-9].

To date, various non-invasive imaging and invasive methods such as computed tomography (CT), magnetic resonance imaging (MRI), ultrasound (US) and intravascular ultrasound (IVUS) have been widely used clinically [10-15]. These approaches have advantages in terms of spatial resolution and the ability to identify in detail morphological alterations such as calcifications and vessel stenosis, a degree of which is retained by compensative outward dilation of the vessel, especially in the early phase of atherosclerosis, and further deteriorates after over 40% of the growth [16]. Thus, such morphological imaging techniques have disadvantages in detecting early/mild atherosclerosis. Furthermore, about 70% of diseases leading to AMI were reported to be those with less than 50% stenosis and 80-90% of the culprit lesions for infarction were those with less than 70% stenosis [17]. Therefore, the functional discrimination of plaque instability rather than the degree of stenosis is essential for early diagnosis and treatment. Although efforts have been made towards detecting unstable plaques using these morphological imaging techniques, they require skill or expertise to distinguish the plaque properties, which could make quantitative estimation challenging. On the other hand, nuclear imaging techniques such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) can noninvasively collect quantitative information on the expression levels of functional molecules and metabolic activities in vivo and thus provide functional diagnoses of unstable plaques with high sensitivity [18].

In this paper, we review the present state and future of radiolabelled probes (Figures 1 and 2) that have been developed for detecting unstable atherosclerotic plaques using nuclear imaging techniques [2, 3, 19-24].

Probes to detect macrophage activity

2-[18F]Fluoro-2-deoxy-D-glucose ([18F]FDG) is taken up by cells via the glucose transporter and trapped inside cells after phosphorylation by hexokinase [25]. [18F]FDG has proven to be
useful in varied clinical fields including diagnosis, prediction and measurement of treatment effectiveness in tumors, myocardial infarction, and epilepsy, making it one of the most commonly used probes in nuclear medicine [26-29]. In unstable plaques, an abundance of invading macrophages causes inflammation that makes plaques vulnerable to rupture. Therefore, specific imaging of macrophages is effective for diagnosing unstable plaques in atherosclerotic lesions. Since glucose metabolism is active in macrophages, $^{18}$F-FDG has been used widely for basic and clinical studies [27].

In a basic study using a rabbit model, myocardial infarction-prone Watanabe heritable hyperlipidemic rabbits (WHHLMI rabbit), which present atherosclerotic lesions similar to those seen in humans [30-32], significantly higher accumulation of $^{18}$F-FDG in WHHLMI rabbit vessels than that in normal New Zealand White rabbit vessels was observed. Also, the probe accumulation in vessels of model rabbits was related to the quantity of macrophages and not intimal thickening, indicating that $^{18}$F-FDG can diagnose unstable plaques as it detects invading macrophages [33]. In fact, the usefulness of $^{18}$F-FDG to detect unstable plaques has been indicated by several clinical studies [34-36].

Since several statins reduce cholesterol levels in the blood but do not directly affect the accumulation of invading macrophages in atherosclerotic lesions [37, 38], $^{18}$F-FDG imaging to
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Diagnose the vulnerability of lesions during drug treatment should be useful for planning subsequent treatments as well as aiding drug development in clinical trials. In studies where rabbits were treated with probucol, $^{[18]}$F-FDG uptake in the atherosclerotic vessels decreased along with reductions in macrophages [39-41]. In clinical trials to develop atherosclerotic drugs, $^{[18]}$F-FDG imaging was used as an imaging biomarker [42]. Despite its usefulness as a probe, care must be taken in evaluating $^{[18]}$F-FDG imaging results because $^{[18]}$F-FDG uptake in vessels can be affected by several factors such as diet and lifestyle changes, as well as drug administration [43].

In addition, plaque-invading macrophages accompany increased construction of cell membranes with proliferative activation, which induces an increase in the uptake of choline, a constituent of the cell membrane. Thus, $^{[11]}$C choline and the $^{18}$F labeled choline analog ($^{[18]}$F fluoro choline ($^{[18]}$FCH)) were evaluated for their ability to detect unstable plaques and both were reported to image unstable plaques with higher sensitivity than $^{[18]}$F-FDG [44-46]. Fatty acids are a common constituent of atherosclerotic plaques and are synthesized in the plaque. Since a main substrate of fatty acid synthesis is acetyl-coenzyme-A, which is produced from acetate [47], $^{[14]}$Cacetate PET may have the potential to provide additional information for characterizing atherosclerotic plaques, similar to its current use in imaging procedures used to evaluate tumors and myocardial oxidative metabolism [48]. Indeed, the feasibility of $^{[14]}$Cacetate PET for imaging arterial wall alterations has been demonstrated in a cohort of asymptomatic patients [49].

Probes to detect LOX-1

Lectin-like oxidized LDL receptor-1 (LOX-1) is a receptor for oxidized LDL and is expressed on

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**Figure 3.** Planar images of WHHLMI and JW rabbits at 10 min and 24 hr post administration of $^{99m}$Tc-LOX-1 mAb and subclass-matched control antibody ($^{99m}$Tc-IgG$_2a$). The atherosclerotic abdominal aorta was clearly visible 24 hr post administration in the WHHLMI rabbits given $^{99m}$Tc-LOX-1 mAb while high blood pool radioactivity in the abdominal aorta was shown in every rabbit at 10 min. Arrows = aorta; K = kidney; L = liver; S = spleen.
vascular endothelial cells, smooth muscle cells, monocytes, and macrophages in atherosclerotic lesions. LOX-1 is related to lesion progression and induces development of plaques and destabilization by several mechanisms: 1) induction of cell adhesion molecule and leucocyte chemotactic factor expression on the surface of vascular endothelial cells; 2) facilitation of foam cell formation from macrophages; 3) induction of apoptosis in smooth muscle cells (spontaneous cell death); and 4) induction of matrix metalloproteinases (MMP) that degrade the extracellular matrix in plaques [50-57]. Therefore, LOX-1 is an important target for nuclear imaging. In fact, the instability of atherosclerotic plaques was reported to be highly correlated with LOX-1 expression in a WHHLMI rabbit model [58].

A radiolabeled probe for LOX-1, 99mTc labeled monoclonal antibody (99mTc]anti-LOX-1 mAb), was evaluated in WHHLMI rabbits [59]. As expected from the expression profile of LOX-1 in atherosclerotic vessels, [99mTc]anti-LOX-1 mAb, which recognizes the LOX-1 protein extracellular domain as its epitope, could detect atherosclerotic vessels in WHHLMI rabbits in planar imaging when compared with control rabbits (Figure 3). In addition, the radioactivity accumulation in vessels was correlated with the instability index of lesions estimated from immunohistochemical staining and the specificity of accumulation in unstable lesions was higher than that of [18F]FDG. Another example of the use of LOX-1 as a targeting probe was a liposome probe coated with anti-LOX-1 mAb on its surface as a targeting moiety and loaded with 111In, Gd, and fluorophores as signal emitting moieties for multimodality imaging [60]. In vivo evaluation using ApoE knock out mice revealed that this multifunctional probe could image atherosclerotic lesions by MRI, as well as with optical and nuclear imaging. In accordance with results from a previous study, radioactivity accumulation was related to LOX-1 expression, macrophage existence, apoptosis occurrence, and MMP-9 expression, indicating that LOX-1 is a promising target for evaluating unstable plaques in in vivo imaging. Another scavenger receptor, CD68, has been studied as a target for molecular imaging. 124I labeled CD68 conjugated to an Fc-fragment was evaluated as a tracer in ApoE knock out mice to indicate the enhanced radioactivity in aortic lesions by ex vivo autoradiographic analysis [22].

Probes to detect apoptosis

During atherosclerosis progression, macrophage apoptosis contributes to the formation of the lipid core of plaques while smooth muscle cell apoptosis destabilizes the plaque's fibrous cap by suppressing extracellular matrix formation [61, 62]. As such, apoptosis imaging is useful for evaluating the instability of atherosclerotic lesions. [99mTc]Annexin A5 was developed as an imaging agent for apoptosis due to its ability to bind to phosphatidyl serines that typically reside in the inner leaflet of cell membranes and become exposed on the outer surface of cell membranes during apoptosis [63-66]. [99mTc]Annexin A5 has also been widely used in atherosclerotic imaging [67-70] and reportedly can image unstable plaques more specifically than [18F]FDG [71]. The accumulation of [99mTc]Annexin A5 in atherosclerotic plaques represents the treatment efficiency of caspase inhibitors [70]. While apoptosis has been recognized as a promising target to estimate atherosclerosis in studies with [99mTc] Annexin A5, low molecular weight probes such as [18F] labeled isatin derivatives have also been developed recently [72, 73].

Probes to detect MMP

Unstable plaques are morphologically characterized by a thin fibrous cap that overlays a large lipid core. MMPs degrade the extracellular matrix that constitutes this fibrous cap, resulting in plaque destabilization [74-76]. MMPs can be divided into two groups: soluble and membrane-bound [77-79]. Most soluble MMPs, including MMP-2 and MMP-9, require extracellular post-translational cleavage to become biologically active following release from cells. A membrane-bound MMP, membrane type-1 matrix metalloproteinase (MT1-MMP or MMP-14), mediates activation of MMP-2 and MMP-13 on the cell surface. Increased expression of MMP-2 and MMP-9 has been observed in human atherosclerotic lesions [74, 80, 81] and these MMPs are known to cleave native type IV, V, VII, and X collagens and elastin, as well as the degradation products of collagens types I, II, and III after proteolysis by collagenases such as MMP-1 and MMP-13. In a recent animal study, co-distribution of MT1-MMP and MMP-2 was demonstrated in grade IV atheroma, indicating a possible...
role for MT1-MMP in the destabilization of atherosclerotic plaques [82], which is supported by MT1-MMP expression that was observed in human atherosclerotic plaques [83, 84]. Thus, MMPs are potential targets for diagnostic imaging of atherosclerotic plaques that are at higher risk for rupture [85, 86]. In the development of MMP imaging probes, the following three approaches have been pursued.

The first strategy involves radiolabelled MMP substrates that remain within the lesions after degradation by activated MMPs [87] and was used in one of the first attempts to image MMP activity in vivo for optical imaging of tumor-associated MMP activity. The resulting imaging probe was a kind of smart probe containing a MMP-2 peptide substrate with quenched near-infrared fluorochromes that are cleaved upon recognition by the MMP [88]. Recently, an activatable SPECT imaging probe specific for MMP-14 using a cell penetrating peptide as the retention moiety in the cells after MMP recognition was reported to be partly successful in in vitro experiments [89].

The second strategy uses radiolabelled MMP inhibitors such as [99mTc]RP805 (MPI) and [111In]RP782, which have been shown to have higher accumulation in vessels of apoE KO mice as compared to control mice [90, 91]. The vessel accumulation of [99mTc]RP805 was reported to be correlated with the expression of MMP-2, -9 and macrophages and is effective for assessing the treatment effect of statins [92]. In addition, since MMP-2 and MMP-9 expression was higher than the rate of apoptosis in progressive atherosclerotic lesions in apoE KO mice, [99mTc]RP805 was presumed to be more useful for evaluating later stages of atherosclerosis than is [99mTc]Annexin A5 [93]. Further, low uptake of [99mTc]RP805 in the myocardium provided another advantage over [18F]FDG to yield high S/N ratios for imaging of coronary arteries [22].

The third strategy involves radiolabelled monoclonal antibodies such as [99mTc] labeled monoclonal antibodies specific for membrane-bound MMPs ([99mTc]anti-MT1-MMP mAb) [94]. In a recent study comparing MMP-2 with MT1-MMP, MT1-MMP was reported to be expressed specifically in unstable lesions that are prone to rupture, indicating its potential use as a target for molecular imaging [82]. Indeed, [99mTc]anti-MT1-MMP mAb accumulated in unstable

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**Figure 4.** Planar images of WHHLMI and JW rabbits at 10 min and 24 hr post administration of [99mTc]-MT1-MMP mAb and subclass-matched control antibody ([99mTc]-IgG3). The atherosclerotic abdominal aorta was clearly visible 24 hr post administration in the WHHLMI rabbits given [99mTc]-MT1-MMP mAb while high blood pool radioactivity in the abdominal aorta was shown in every rabbit at 10 min. Arrows = aorta; K = kidney; L = liver; S = spleen.
lesions (grade IV atheroma) specifically in the vessels of WHHLMI rabbits (Figure 4) [94].

Together with the studies described above, MMPs have long been recognized as important targets for evaluating atherosclerotic plaque instability. Other MMP subtypes such as MMP-12 have recently attracted a great deal of attention as a target for atherosclerosis treatment [95], with recent studies indicating a detrimental role for MMP-12 in plaque progression and instability in both mouse [96] and rabbit models [97, 98] and an association between MMP-12 expression and advanced human atherosclerotic lesions [99, 100]. Also, treatment of apoE KO mice with selective MMP-12 inhibitors could retard atherosclerosis development resulting in a more fibrous plaque phenotype [95], indicating that development of a MMP-12-selective imaging probe would be desirable for diagnosis and/or prediction of atherosclerosis and selection of drug treatments. In general, the complex relationship between MMP activity and plaque stability has made understanding the roles of each MMP subtype in atherosclerosis challenging, and the close structural similarity of the MMP active sites has made developing highly selective MMP inhibitors difficult. However, recent advances in novel peptide chemistry have made it possible to provide more selective inhibitors of zinc-proteases and this strategy could also be applied for developing selective MMP inhibitors [101].

**Probes to detect thrombus formation**

Thrombus formation triggered by plaque rupture is the most important mechanism leading
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to the onset of AMI and ischemic sudden death. Thus, thrombus-forming vulnerable plaques are a clinically important target for estimating risk and providing more effective and precise treatments. Tissue factor (TF) initiates the exogeneous blood coagulation cascade that leads to thrombus formation in vivo. Although TF in atherosclerotic lesions was identified in several cell types, including endothelial cells, smooth muscle cells, monocytes, macrophages, and foam cells [102], TF expression is reported to be increased in the later stages of atheromatous progression and thus was selectively detected in atheromatous lesions in both animal and human studies [103, 104]. In the blood coagulation cascade, TF initiates the cascade, while factor XIII covalently cross-links fibrin polymers and renders the thrombus more resistant to lysis.

The use of a \(^{99m}\text{Tc}\)-labelled anti-TF monoclonal antibody as a TF imaging agent was recently reported [105]. In ex vivo experiments using WHHLMI rabbits, a close relationship between probe accumulation and TF expression in lesions and the selective accumulation of the probe in atheromatous lesions was indicated. Thus, imaging of TF has the potential to selectively detect atheromatous plaques that are at higher risk for rupture. Figure 5 illustrates the expression profiles of LOX-1, MT1-MMP, and TF that were evaluated under the same experimental conditions as those used previously with WHHLMI rabbits [59, 94, 105]. Although each of the three molecules is expressed mainly in atheromatous lesions, TF is the most selective in rupture-prone lesions, while the LOX-1 profile is closely related to macrophage distribution. On the other hand, a series of imaging agents have targeted fibrin and factor XIII in thrombi using antibodies or peptides [106]. EP-2104R, an 11-amino-acid peptide conjugated to four gadolinium-tetraazacyclododecane tetraacetic acid moieties (Gd-DOTA), binds fibrin with micromolar affinity and can detect thrombi in vivo in pigs and patients using a clinical 1.5T whole-body MRI system with high-signal amplification [107-109]. Probes that conjugate a factor XIII substrate peptide to fluorochromes or \(^{111}\text{In}\)-chelates were reportedly able to visualize factor XIII activity in clotted human plasma in vitro, and in acute murine thrombi induced by FeCl\(_3\) [110, 111]. Since \(P^1, P^2\)-monochloromethylene diadenosine-5′, 5′′-diphosphate (AppCHClppA) is a competitive inhibitor of adenosine diphosphate-induced platelet aggregation, the \(^{18}\text{F}\) labeled analog (\(^{18}\text{F}\)AppCHFppA) has then been studied as an imaging probe that can accumulate in macrophage-rich atherosclerotic plaques in rabbit models and thus may merit further evaluation [112]. Although further studies are required to investigate which target molecule(s) in the blood coagulation cascade are the most appropriate for estimating the in vivo vulnerability of a plaque, \(^{99m}\text{Tc}\)-anti-TF mAb will be useful for early detection of the cascade while fibrin and factor XIII imaging probes can detect later stages and thrombi themselves. Furthermore, given the great efforts that have been made in developing anti-coagulation and anti-platelet pharmaceuticals for treating atherosclerosis and hyperlipidemia, effective imaging probes that target blood coagulation cascades are also required for efficient drug development.

Probes to detect intraplaque angiogenesis

While inflammation is considered to be a key feature of plaque progression, intraplaque angiogenesis mediated by proliferation of the medial vasa vasorum has also been recently implicated in rapid plaque growth and plaque rupture [113]. The fragile neovasculature structure may lead to extravasation of blood components with subsequent intraplaque hemorrhage leading to plaque rupture. Thus, angiogenesis and inflammation within atherosclerotic lesions may be an important target for molecular imaging.

\(^{[18]}\text{F}\)Galacto-RGD is a peptide tracer that binds to \(\alpha\text{v}\beta3\) integrin, a cell surface glycoprotein receptor that is highly expressed during angiogenesis. \(^{[18]}\text{F}\)Galacto-RGD PET has been extensively validated for imaging of angiogenesis in tumors [114]. Dosimetry of \(^{[18]}\text{F}\)Galacto-RGD has already been evaluated in humans based on PET imaging data that indicated a radiation dose comparable to that of \(^{[18]}\text{F}\)FDG, so that \(^{[18]}\text{F}\)galacto-RGD can safely be used for integrin \(\alpha\text{v}\beta3\) imaging [115]. Since both macrophages and activated endothelial cells can express high levels of \(\alpha\text{v}\beta3\) integrin in atherosclerotic lesions, \(^{[18]}\text{F}\)galacto-RGD PET has the potential for imaging angiogenesis in atherosclerotic lesions. In a study using hypercholesterolemic mice fed a western diet [116], \(^{[18]}\text{F}\)galacto-RGD
demonstrated specific uptake in atherosclerotic lesions that was associated with macrophage density. Furthermore, an in vivo PET imaging experiment showed $[^{18}F]$galacto-RGD uptake that co-localized with calcified lesions of the aortic arch as indicated by CT angiography. Thus, $[^{18}F]$galacto-RGD is a potential tracer for noninvasive imaging of atherosclerotic lesions. A $^{99m}$Tc labeled Cy5.5-RGD imaging peptide (CRIP) [117] was also developed for assessing cardiac remodeling after myocardial infarction and its responsiveness to anti-angiotensin treatment. In addition, atrial natriuretic peptide and C-type natriuretic peptide have recently been demonstrated to attenuate angiogenesis and have been widely investigated for their therapeutic potential. Thus, the clearance receptor (NPR-C) has been recognized as an ideal target for imaging the anti-angiogenic effect of NPs, followed by the development of imaging probes such as $^{64}$Cu labeled peptide probe and $^{64}$Cu labeled peptide conjugate nanoprobe [118, 119], which have been used in mice and rabbit models for imaging NPR-C in angiogenesis.

Intraplaque inflammation plays an important role in the progression and destabilization of atherosclerotic lesions [120]. $[^{11}C]$PK11195 is a specific ligand of the translocator protein (TSPO), which is highly expressed in activated cells of the mononuclear phagocyte lineage [121]. $[^{3}H]$PK11195 was recently reported to show specific binding to macrophages in human carotid endarterectomy samples [122] and $[^{11}C]$PK11195 can be used with CT angiography in humans to assess vascular inflammation in carotid atherosclerotic plaques in vivo [123, 124]. In addition, $[^{68}$Ga]Galectin has traditionally been used to image inflammation with gamma cameras, while $[^{68}$Ga]gallium has been applied for imaging macrophage-rich areas in inflammatory lesions in mice [125]. Although that study indicated a moderate uptake in the plaques, especially at the sites rich in macrophages, the slow blood clearance may limit this probe's usefulness for clinical imaging of atherosclerotic plaques.

**Probes for other targets**

In addition to the probes described above, $^{99m}$Tc, $^{111}$In, or $^{18}F$ labeled LDL [126-129], which exploit the important role of LDL in plaque progression especially in the early phase, $^{111}$In-oxine labeled monocytes [130], $^{18}F$ labeled small vascular cell adhesion molecule (VCAM)-1 affinity ligand ($[^{18}F]$4V) [131], and radiolabeled cytokines such as IL-2 [132] and MCP-1 [133], which rely on the close relationship between the occurrence of vessel inflammation and plaque progression have also been studied. Furthermore, researchers have recently been investigating the use of nanoparticles as a fundamental part of molecular probes for MRI and optical imaging, as well as for nuclear medicine [134].

**Conclusion**

Although a variety of molecular probes have been developed for molecular imaging of atherosclerotic lesions, only $[^{18}F]$FDG and $[^{99m}$Tc] annexin A5 have had successful clinical applications. One possible obstacle for probe development would be low signal levels in the lesion that may be due to inefficient probe delivery to the lesion. Drug delivery systems that use nanocarriers such as liposomes, micelles, and monoclonal antibodies as well as multimerization of targeting moieties like RGD probes typically used in tumor imaging [114] can be beneficial strategies for facilitating development of atherosclerotic lesion probes. In a clinical setting, a large variety of imaging strategies have been utilized for imaging of atherosclerosis, such as nuclear medical techniques (PET and SPECT), MRI, US, and optical imaging. Nuclear medical techniques are advantageous owing to their high sensitivity and high quantitative capacity to noninvasively provide biological information on molecules that deteriorate in atherosclerotic processes deep within the human body. In addition, results from PET and SPECT noninvasive whole body imaging in animals can be translated to use in humans while optical imaging can only be used in animal imaging and may be difficult to quantify. Furthermore, PET is more sensitive than SPECT and probes in tracer amounts can be detected by in vivo PET imaging, which may minimize the possibility of pharmacological effects and target saturation and in turn be important for molecular imaging in atherosclerosis because the expression of target molecules in lesions is usually low. Continued progress in probe development, especially for PET, is urgently needed for successful disease prevention and patient treatment strategies.
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