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Current advances in the imaging of atherosclerotic vulnerable plaque using nanoparticles

Ming Zhang [a,1], Zhongjian Xie [b,c,1], Haijiao Long [d], Kun Ren [e], Lianjie Hou [a], Yu Wang [a], Xiaodan Xu [f], Weixing Lei [g], Zhicheng Yang [a], Shakeel Ahmed [h], Han Zhang [i,*], Guojun Zhao [a,**]

[a] The Sixth Affiliated Hospital of Guangzhou Medical University, Qingyuan People's Hospital, Qingyuan, 511500, Guangdong, China
[b] Institute of Pediatrics, Shenzhen Children's Hospital, Shenzhen, 518038, Guangdong, China
[c] Shenzhen International Institute for Biomedical Research, Shenzhen, 518116, Guangdong, China
[d] Xiangya Hospital, Central South University, Changsha, 421001, Hunan, China
[e] Institute of Clinical Medicine, The Second Affiliated Hospital of Hainan Medical University, Haikou, 570100, Hainan, China
[f] Department of Pathology, The First Affiliated Hospital of Anhui Medical University, Hefei, 230032, Anhui, China
[g] Guilin Medical University, Guilin, 541199, Guangxi, China
[h] College of Physics and Optoelectronics Engineering Shenzhen University, Shenzhen 518060, China
[i] Key Laboratory of Optoelectronic Devices and Systems of Ministry of Education and Guangdong Province, College of Physics and Optoelectronic Engineering, and Otolaryngology Department and Biobank of the First Affiliated Hospital, Shenzhen Second People's Hospital, Health Science Center, Shenzhen University, Shenzhen, 518060, China

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ABSTRACT

Vulnerable atherosclerotic plaques of the artery wall that pose a significant risk of cardio-cerebral vascular accidents remain the global leading cause of morbidity and mortality. Thus, early delineation of vulnerable atherosclerotic plaques is of clinical importance for prevention and treatment. The currently available imaging technologies mainly focus on the structural assessment of the vascular wall. Unfortunately, several disadvantages in these strategies limit the improvement in imaging effect. Nanoparticle technology is a novel diagnostic strategy for targeting and imaging pathological biomarkers. New functionalized nanoparticles that detect hallmarks of vulnerable plaques are promising for advance further control of this critical illness. The review aims to address the current opportunities and challenges for the use of nanoparticle technology in imagining vulnerable plaques.

1. Introduction

Atherosclerosis, characterized by the formation of plaques causing progressive degeneration of the vessel wall, is the primary pathogenic basis underlying coronary and cerebrovascular diseases [1]. In general, the phenotypes of most atherosclerotic plaques are stable. On the one hand, one may experience a long symptom-free period or just mild stenosis in the bloodstream. On the other hand, the vulnerable plaque phenotype can trigger sudden and life-threatening events, including myocardial infarction or stroke, the leading cause of mortality worldwide. This imposes an enormous burden on society [1–4]. Despite widely promoting remediation interventions, the cardiovascular episodes continually yield substantial consequences [5]. Thus, advanced interventions before the clinical manifestation are necessary and the role of imaging of vulnerable plaques must be highlighted in this context.

The role of routine imaging platforms for the detection of atherosclerotic plaques, including computed tomography (CT), magnetic resonance imaging (MRI), ultrasound and so on, has been evaluated. their ability to distinguish the vulnerable from the stable plaques remains unsatisfactory. Theoretically, the reason can be attributed to the fact that the existing imaging methods essentially rely on the presence of structural abnormalities. However, most commonly, many plaques with suspicious structural abnormalities might not lead to rupture. In addition, there are some limitations to the current imaging platforms, including invasiveness, insufficient coverage breadth, and spatial resolution, which should be considered. Therefore, in the future, a new imaging technology to identify vulnerable plaques warrants attention. It is expected to bring substantial improvements to the protocols of screening, follow-up, and

* Corresponding author.
** Corresponding author.
E-mail addresses: hzhang@szu.edu.cn (H. Zhang), zhaoguojun@gzhmu.edu.cn (G. Zhao).
[1] These authors contributed equally to the work.

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clinical intervention.

In addition to the structural imaging, molecular imaging is increasingly playing an innovative role in the early diagnoses of several diseases. Given that typical pathogenic processes occur during the formation of vulnerable plaque, probes targeting specific biological features are expected to provide additional information on the suspected plaques. Thanks to that, breakouts may advance our ability to diagnosis vulnerable plaques.

Nanotechnology is rapidly evolving in imaging science domain. The detectable characteristics, targeting capability and pharmaceutical stability of nanoparticles confer them with properties of exceptional contrast agents. Over the past decades, advancements in medicine based on nanoparticles have received tremendous attention, especially for the treatment and diagnosis of cancer. Recently, the application of nanoparticles and their promising value for imaging atherosclerotic plaques has been brought forth. Numerous high-quality studies using various bioengineering designs are employed. However, only a few studies emphasize their peculiar function in distinguishing the vulnerable from the stable atherosclerotic plaques, wherein, the design principle is to target and visualize the specific features of the vulnerable plaques. In this review, we focus on the strengths and current challenge in nanoparticle-mediated vulnerable plaque imaging based on the specific hallmarks (Fig. 1).

2. Basic conception of vulnerable plaque

The formation of atherosclerotic plaques arises from cholesterol deposition and lipoprotein retention, gradually evolving into progressive inflammation. Other multifaceted mechanisms include leukocyte recruitment, foam cell transformation, programmed cell death, and smooth muscle cell proliferation [6]. The complex and uneven development of these mechanisms yields heterogeneous hallmarks and functional outcomes in these plaques.

A vulnerable plaque is described as a special phenotype of atherosclerotic plaques associated with a high risk. Unlike stable plaques, the vulnerable plaques are not limited to stenosis, even though they can contribute to more than 60% stenosis area of the lumen [7]. The vulnerable plaques located in the unobstructed lumen can also rupture or activate thrombosis suddenly, resulting in the majority of the acute cardiovascular and cerebrovascular episodes [8,9]. Thus far, most evidence on the biological features of vulnerable plaques is from the rupture-prone plaques owing to their distinctive features [10].

3. The hallmarks of vulnerable plaque

Consensus on the concept indicates that the basic morphological hallmarks of vulnerable plaques focus on the fibrous cap and the necrotic

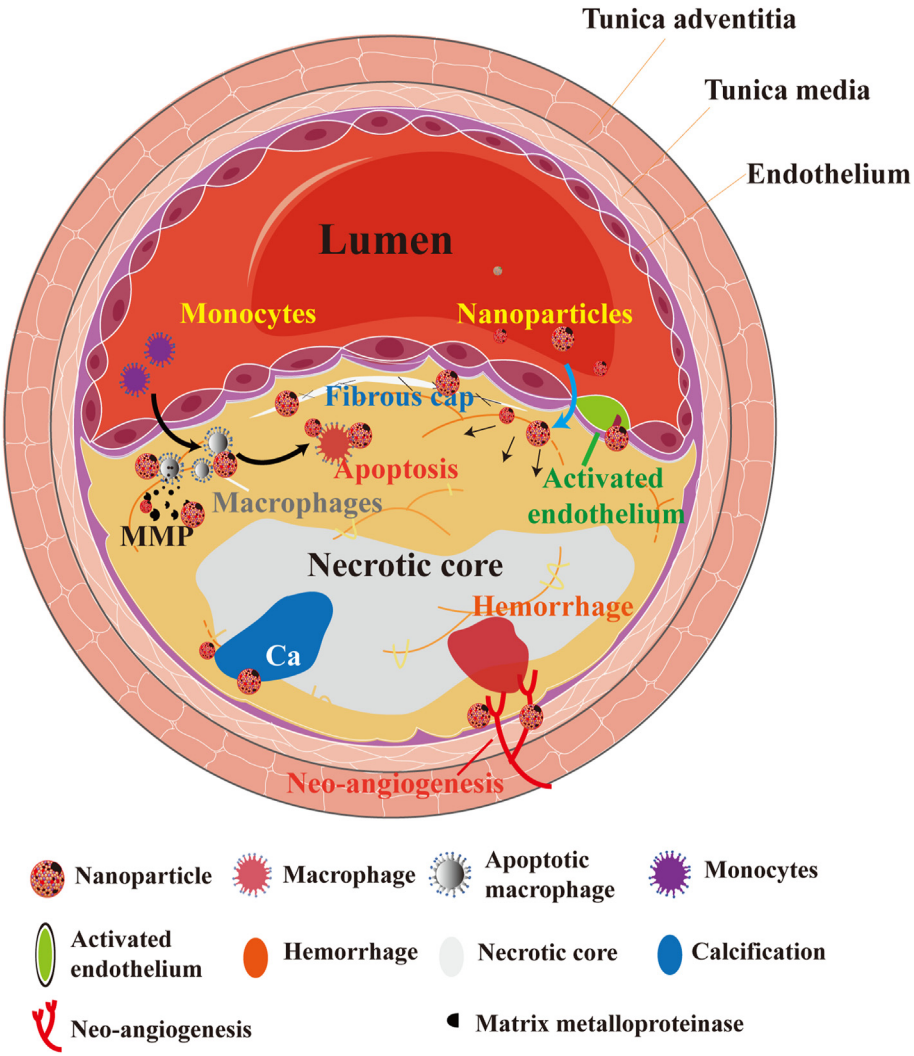

Fig. 1. Schematic representation of nanoparticle technology in the imaging of vulnerable atherosclerotic plaques. Several pathological factors contribute to the thinning of the fibrous cap and the enlargement of the necrotic core, thereby leading to the formation of vulnerable plaque in the vessel wall. These include infiltration of macrophages, release of hydrolytic enzymes (matrix metalloproteins, MMPs), collagen alterations, apoptosis of macrophages, calcification, intraplaque hemorrhage, neo-angiogenesis and activation of the endothelium. Synthetic nanoparticles enter the plaques and bind to the aforementioned pathological factors. Using magnetic resonance and other equipment, nanoparticles accumulate resulting in the imaging of the suspected plaque.

core [11], the essence of which causes the imbalance in forces in vulnerable plaques. If the resistance of the fibrous cap is overcome by the outward expansion of the necrotic core, the probability of rupture becomes considerably high. The underlying mechanism is attributed to the thinning of the fibrous cap or/and an enlargement in the necrotic core. Accumulating evidence suggests that several cells and molecules contribute to fibrous cap thinning or necrotic core enlargement. These have been documented as the biological hallmarks for assessing the vulnerable plaques [12].

3.1. The hallmarks of fibrous cap thinning

The thinning of the fibrous cap reduces the tolerance of plaque, thus increasing the possibility of a rupture. Thus, the exposure of the necrotic core lying beneath the fibrous cap to blood leads to thrombus and ischemia [13]. At least three mechanisms underlying the thinning of the fibrous cap have been confirmed.

First, macrophages are recruited into the lesion, which is the primary mechanism for the thinning of the fibrous cap [14]. Phenotypes may change due to macrophage polarization, causing pro-inflammatory effects [15,16]. It has been postulated that inflammation favors the formation of vulnerable plaque and is also associated with clinical outcomes [17]. As a proof of principle, pathological studies confirm the abundance of macrophages in the ruptured or rupture-prone plaques [18,19].

Second, the proteolytic enzymes secreted by the recruitment of immune cells directly affect fibrous cap thinning. In particular, matrix metalloproteinases (MMPs), can degenerate and hydrolyze the components of the matrix in a neutral pH environment [20,21]. Increasing evidence supports that despite differences in MMPs among species and animal models, the important role of these enzymes is executed [21]. Indeed, the level of MMPs that destabilized the coronary plaque may result in acute coronary syndrome [22].

Lastly, the inward resistance of apical cap in plaques is mainly dependent on the tight connective tissues of the arterial intima [23]. Collagen belongs to a classic family of proteins whereby long stretches unfold in fibrous formatio [24]n. During plaque progression, the connective tissue often adaptively thickens [23]. The collagen-rich tissue, mainly enriched with collagen type I, and the proliferation of smooth muscle cells facilitates plaque stabilization. Conversely, a reduction in fiber collagen is a hallmark of plaque vulnerability [25]. Therefore, assessing the expression or amount of collagen during fibrous formation is representative of the thickness of the fibrous cap. In addition, another member of the collagen family, type IV collagen, is known to be the most abundant component occupying half of the area of the vascular basement membrane [24]. The exposure of collagen IV indicates increased permeability during plaque formation [26]. Thus, a change of collagen thickness or its exposure is an interesting hallmark for accessing the plaque.

Taken together, the morphological and molecular features of fibrous cap thinning, including macrophages recruitment, overexpression of MMPs, and changes of in collagen are implicated as potential biomarkers of a vulnerable plaque.

3.2. The hallmarks of necrotic core enlargement

The expansion of necrotic core inside vulnerable plaque is also known to be responsible for the rupture. A necrotic core is defined as the accumulation of lipid and foam cells in the intima. The enlargement of the necrotic core irreversibly destroys the tight tissues, leaving behind a loose gruel of lipids. Several following factors contribute to the enlargement of the necrotic core.

First, the theory of necrotic core development supports that apoptosis in macrophages and smooth muscle cells plays play important roles. At an early stage during plaque formation, apoptosis inhibits cell transformation into foam cells as an endogenous protective mechanism [27]. However, further enrichment of lipid and lipoprotein cause excessive apoptosis, leaving too many remnants in the lesion, due to the defective efferocytosis, eventually exacerbating necrosis and enlargement of the necrotic core [28,29]. Indeed, previous studies address that regulation of macrophage apoptosis prevents plaque rupture [30]. Beside, several pieces of evidence suggest apoptosis as a hallmark to evaluate the vulnerability of plaques [31].

Second, calcification is a common component in the advanced plaques, especially among the elderly [32]. According to histological reports, owing to the accumulation in the matrix and necrotic core, lumps and plates of calcium deposits increase the volume in the intima [33]. Furthermore, the localization of calcium deposits is positively correlated with vulnerability [34]. Although studies evaluating the pivotal role of the calcification as a hallmark mainly focus on the coronary artery and aortic diseases, nevertheless, they confirm its involvement in elevating cardiovascular risk [35].

Third, the reason underlying enhanced plaque vulnerability due to intraplaque hemorrhage is the rapid increase in the volume of plaque [36]. In addition, the extravasation of the blood into plaque also results in the accumulation of iron, cholesterol, and hemoglobin, which in turn, promotes the development of plaque due to reactive oxygen species and inflammation [37]. According to a recently published meta-analysis, the presence of intraplaque hemorrhage increases the risk of future stroke regardless of gender and stenosis area [38]. Thus, this is among the most reliable morphological hallmarks associated with the potential risk of cerebrovascular events.

Finally, neo-angiogenesis is another independent risk factors for the vulnerability of plaques. These deficient blood vessels which originate from the adventitia and extend to the base of plaque are more susceptible to rupture [39]. Moreover, they facilitate the entry of inflammatory cells because of their loose endothelium [40]. These sequential events result in hemorrhage and inflammation as outcomes [41]. A clinical study confirms increased progression of clinical symptoms in presence of angiogenesis [42]. Nowadays, the best molecular hallmarks to target neo-angiogenesis are αvβ3 and vascular endothelial growth factor (VEFG) [43,44].

3.3. Other hallmark of vulnerable plaques

Despite the aforementioned hallmarks, several other molecules may play a role in the formation of a vulnerable plaque. For instance, endothelial cells are activated and express vascular cell adhesion protein 1 (VCAM-1) in the early stage of vulnerable plaque formation [45]. VCAM-1 binds to the granulocytes and activates intracellular signaling cascade, thereby inducing changes in the shape of endothelial cells facilitating granulocyte migration [10]. An analysis of the carotid plaque specimens demonstrates that the expression of VCAM-1 on the endothelium is indicative of significantly high risk in humans [46]. Similarly, several potential hallmarks, including hypoxia, lipids and proteases, are also under evaluation in the context of vulnerable plaques.

4. Current imaging methods and their limitations of vulnerable plaques

In the light of above-mentioned typical hallmarks, many modalities have been evaluated to improve the diagnostic efficiency of imaging vulnerable plaques. To date, most of these investigations are dependent on the identification of abnormal structures of suspected plaques (Fig. 2).

4.1. Structural imaging and limitations

Traditional platforms, including computed tomographic (CT) scanning and magnetic resonance imaging (MRI) remain the primary methods for imaging plaque lesions.

Accumulated evidence demonstrates that CT scanning can be used for the detection of atherosclerotic burden, stenosis degree, and in particular, plaque calcification of the coronary artery [47,48]. Its advantages

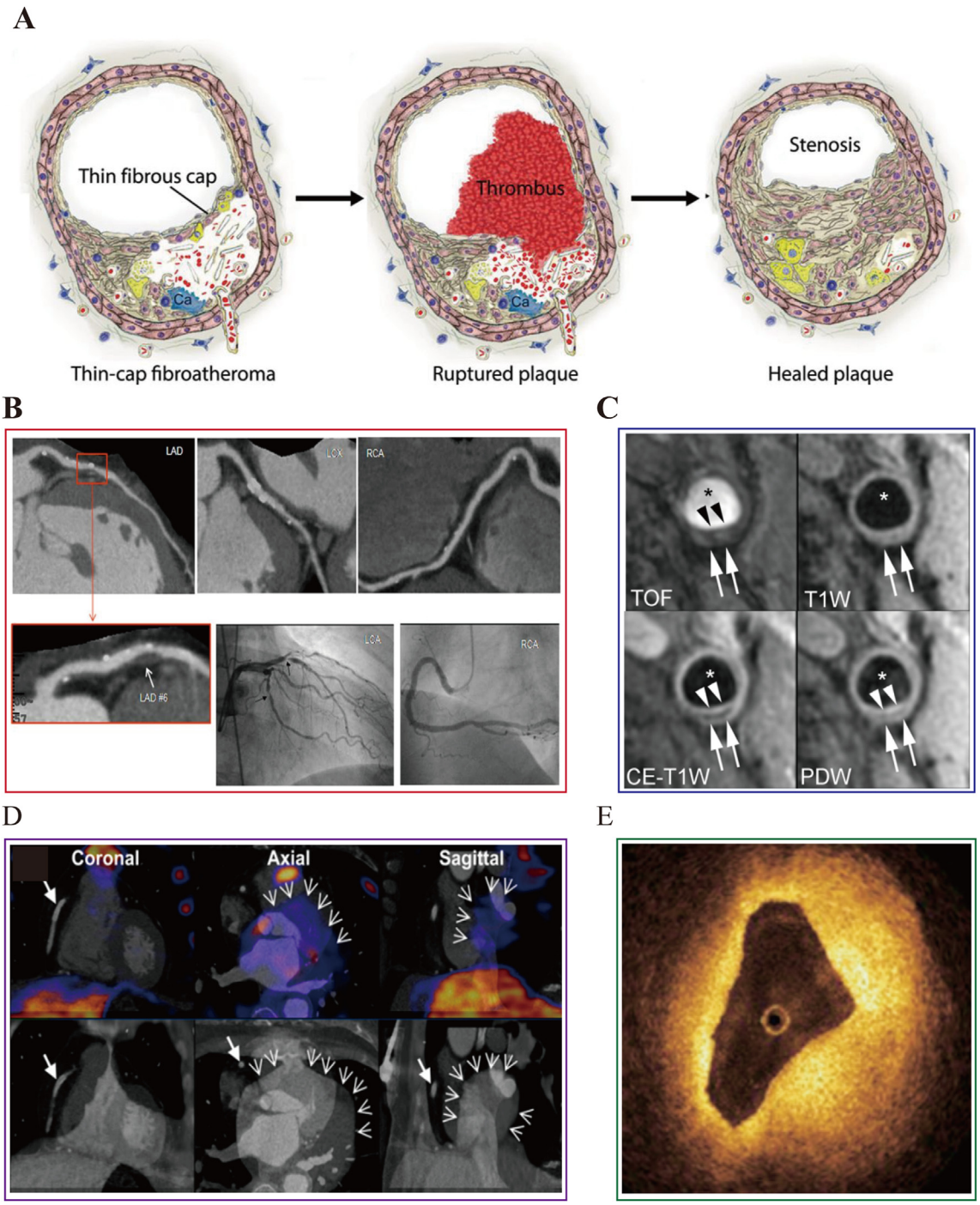

Fig. 2. A figure summarizing the current imaging methods depending on hallmarks of vulnerable plaques. A) A vulnerable atherosclerotic plaque contains a thin cap and a large necrotic core. Reprinted with permission from ref. 11. Copyright 2014 Wolters Kluwer Health. B) CT angiography and reformation images show spotty calcification in the plaque of a patient with acute coronary syndrome. Reprinted with permission from ref. 51. Copyright 2009 American College of Cardiology Foundation. Published by Elsevier Inc. C) A 3T MRI in *vivo* indicates necrotic core (arrows) with thick fibrous cap (arrow heads). Reprinted with permission from ref. 123. Copyright 2009, Wolters Kluwer Health. D) Imaging the stenting site of coronary artery using PET and CTA. Reprinted with permission from ref. 67. Copyright 2012 Society of Nuclear Medicine and Molecular Imaging. E) OCT image shows a fibrous plaque with homogeneous rich signal band. Reprinted with permission from ref. 63. Copyright 2006 Elsevier Inc.

include non-invasiveness and practicality. Thus, it is a widely used screening method to predict the incidence of atherectomy [49]. Nevertheless, there exist some disadvantages. For example, CT scan utilizes radiation posing potential medical risks. Further, the contrast agents that aid in enhanced CT imaging may also cause renal injury [50]. Moreover, due to limited imaging resolution, CT scanning fails to report the fibrotic and lipid components in the plaque, thereby exhibiting a low sensitivity for the identification of a vulnerable plaque [51]. Taken together, CT scanning is often used for the evaluation of coronary artery calcification despite an insufficient spatial resolution for imaging all the microstructures of the lesion.

MR is considered the gold standard for the non-invasive examination of substantive structure [52]. Generally, paramagnetic metallic agents, such as gadolinium reduce the T1 relaxation property, while

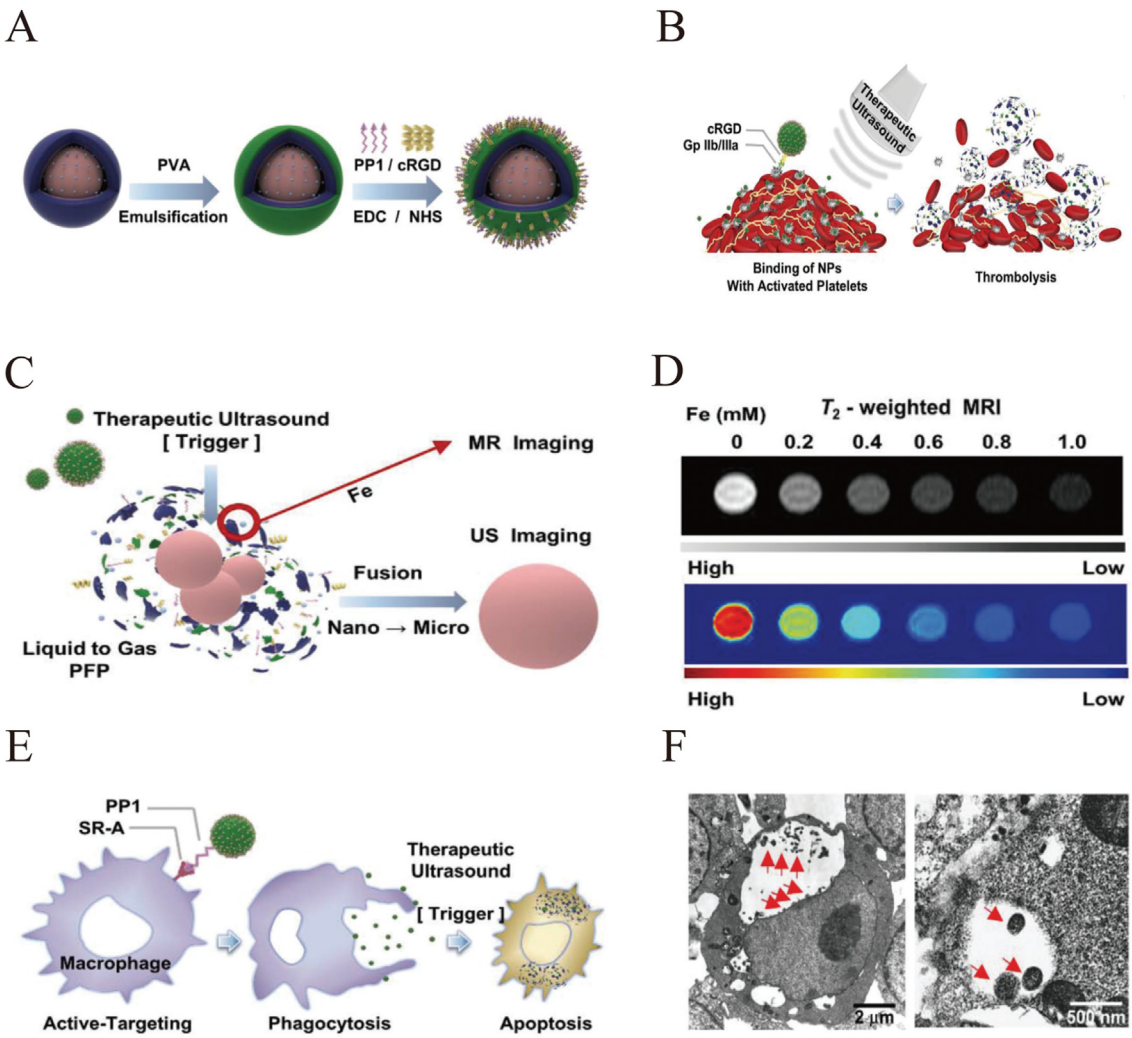

Fig. 3. An examples of nanoparticles functionalized for targeting macrophages the imaging of vulnerable plaques. A) Scheme illustration of the synthesis of multifunctional pathological mapping of theranostic nanoparticles targeting macrophages. B) Treatment of thrombus using nanoparticles. C) Release of Fe for MRI and PFP for US imaging triggered by ultrasound. D) T2-weighted MRI scans by T2W of nanoparticles at various Fe concentrations. E) Scheme illustration of interaction between the nanoparticles and macrophages. F) The images of nanoparticles in macrophages as detected by transmission electron microscopy. Reprinted with permission from ref. 104. Copyright 2021 Royal Society of Chemistry.

super-paramagnetic metallic agents influence the T2 relaxation properties. Owing to these contrast agents, shortened T1 and T2 result in improved signals in the MR scans. Higher resolution for soft tissues as compared to CT scan, yield greater information of vascular structure including necrotic core, fibrous cap, and intraplaque hemorrhage from MRI scans. Moreover, contrast-enhanced MRI further improves the efficiency for the identification of plaque microvasculature, markedly greater than the non-enhanced T-weight imaging [53]. Data from a recent study of vulnerable carotid plaques suggest that MR offers a high-quality comparison in the lesion. However, the direct value of MR for predicting subsequent stroke requires further investigation [54]. Additionally, there are some disadvantages of MRI. First, MRI scans typically take more time, and the imaging procedure for large regions or multiple vessels is difficult, especially due to the dynamical motion artifacts of small vessels [55]. Second, special coils or protocols of vascular scanning are expensive for non-specialized operators or centers [56]. Third, metal implants, often being employed for patients with cardiovascular problems, limit MRI [57]. In general, MR a promising non-invasive modality having a higher resolution for the identification of typical structure of vulnerable plaques.

To overcome the flaws of CT scans and MRI, two technical solutions have been proposed. One of them aims to further enhance spatial resolution. Great efforts have been made in this direction.

To pursue enhanced spatial resolution and the ability to distinguish the plaque volume and structure, some invasive approaches have been designed considering the risk of tolerable complications. Intravascular ultrasound (IVUS) and optical coherence tomography (OCT) are the main platforms among these attempts, are the main leading platforms among these attempts, characterized by catheter-based invasive methods [58]. With regard to the deep penetrating imaging capability, IVUS can offer a real-time and two-dimensional image portrait to identify the necrotic core. In addition, it is a valuable tool to compare volume of plaques in vivo because of its quantification and reproducibility [59]. However, the resolution of IVUS is limited to 100–200 μm, which still limits the imaging of micro biomarkers in the vulnerable plaques, including the thin fibrous cap, micro-calcification, and inflammation [58]. More advanced and specified applications with IVUS, such as virtual histology (VH)-IVUS based on the radiofrequency analysis of ultrasound signals, can detect the presence of calcification [60]. Fluorescence lifetime images (FLIM)-IVUS based on fluorescence spectroscopy technique may enhance the ability to distinguish the thin fibrous cap [61]. Another promising invasive modality, OCT, improves the resolution at 10–20 μm. It can detect thin fibrous caps, micro-calcification, inflammation, and neo-angiogenesis formation, allowing for a reliable evaluation of plaque vulnerability.

Unfortunately, there are some limitations to OCT imaging as well. The major limitation is its low penetration depth which is only 2–3 mm [62]. This implies that OCT imaging in vivo tends to be blocked by the surrounding blood and vessels, making it difficult to obtain an ideal large-scale image. In addition, the OCT imaging often confuse the presence of calcium deposits and lipid pools [63,64]. Therefore, reliable clinical trials are rarely performed to validate if IVUS and OCT constitute a qualified evaluation strategy for vulnerable plaques.

In general, structural imaging is still depending on improving spatial resolution to directly visualize the plaque. Current modalities including MRI and intravascular imaging are well developed for assessing plaque volume or massive structures, such as the necrotic core. However, insufficient resolution and non-specific signal imaging limit their discriminating abilities, along with their respective inadequacies. Therefore, to make microstructures easily identifiable, molecular imaging modalities for vulnerable plaques are evolving rapidly.

4.2. Molecular imaging and limitations

As mentioned previously, the other technical solution to overcome the shortcomings of structural imaging is molecular imaging. In past decades, molecular diagnostic technology has been gaining popularity. It becomes a new trend allowing for characteristically tracing in vivo as a noninvasive method [65,66]. Emerging platforms of molecular imaging are providing a biological evaluation of the ongoing functional status for assessing vulnerability-prone regions.

For molecular imaging, positron emission tomography (PET) is an eligible platform, based on the positron signals emitted from the radio-labeled tracers. Recently, for a series of molecules as markers for vulnerable plaque formation, including inflammation, micro-calcification, angiogenesis, vascular cell adhesion, and collagen loss, it has been demonstrated that these can be traced by PET [67–71]. To better assess vascular inflammation, systems for quantitative assessment using PET has been developed. For example, a perivascular attenuation index is a promising tool for the evaluation of vascular inflammation of human coronary arteries [72]. In addition, novel contrast agents such as ^{68}Ga-labeled somatostatin receptor ligand are in early stage of human studies [73]. Nevertheless, the use of PET for imaging vulnerable plaques remains in the preclinical stage. The following disadvantages are the main causes of concern. First, a low spatial resolution implies that the PET image loses structural information, especially for the tiny blood vessels such as coronary arteries [74]. Second, the undesirable attenuation of signal imposed by the dynamics of cardiac and respiratory affect the observation of subtle lesions [75]. Third, the radiation, cost, equipment maintenance, and other matters should also be taken into consideration [76]. Taken together, it is difficult for PET as a single modality to popularize vulnerable imaging.

Therefore, additional work is required due to the limitations of both structural and molecular imaging platforms. Some advantages and limitations of clinical imaging modalities have been summarized in Table 1. Developing systems drawing on the advantages of both imaging platforms, also referred to as hybrid multimodal imaging, is a potential solution, that is expected to provide the most comprehensive information from imaging of vulnerable plaques [77]. As such, PET/CT and PET/MR facilitating this hypothesis have been purposed for applications. Unfortunately, only very few medical centers implement such instruments. Relatively, the usual MRI or CT scan devices combined with novel contrast agents which are functionalized for molecular tracing have broader impacts [78].

Table 1
Summary of the advantages and limitations of different clinical imaging modalities.

Imaging Modality		Advantages	limitations
Structural imaging	Computed tomography	High specificity. Detection of atherosclerotic burden, stenosis degree and plaque calcification.	Low spatial resolution to distinguish soft tissue.
		High reproducibility.	Risk of exposure to radiation and iodinated contrast agents.
	Magnetic resonance imaging	Greater morphological information, including necrotic core and hemorrhage.	Long scanning time with artifacts due to motion of small vessels.
		No radiation.	Metal implants are limited.
	Intravascular ultrasound	Deeper penetration.	Low spatial resolution. Invasiveness.
		Ability to distinguish luminal dimensions and plaque burden.	Dependence on operator technology.
	Optical coherence tomography	High resolution. Fast data acquisition rate. Visualization of the adjacent tissue.	Low penetration. Invasiveness. Dependence on operator technology.
Molecular imaging	positron emission tomography	Distinguishing micro-calcification, angiogenesis, vascular cell adhesion, and collagen loss.	Not used widely and expensive.
		High sensitivity.	Risk of radiation exposure. Severe loss of structural information.

5. Nanotechnology-based imaging of vulnerable plaques

Nanotechnology is another promising technology platform for molecular imaging [79,80]. Knowledge of the several advantages of this technology for novel contrast agents is well documented. First, the nanoparticles can be used to image the lesions of interest with conventional equipment, whereby metallic elements are synthesized into superparamagnetic or paramagnetic particles. Non-invasive imaging devices that are widely used, including MRI or CT scans, can simultaneously yield structural and molecular information [81]. Second, the surface functionalization and synthesis methods have been highly improved in recent years. The size, shape and electronic charge of nanoparticles are effectively controlled, which directly affect the non-specific uptake, bio-distribution of nanoparticles. PEG or zwitterionic polymers are the most common materials one can use to modify the nanoparticle surfaces [82–84]. Over decades, several nanoparticles-based formulations have been developed, such as polymeric, chitosan, nanogels, nanocapsules and solid lipid nanoparticles and so on [85]. Furthermore, specific peptide can be engineered and coated onto the surface of the nanoparticles. These properties offer high penetration into to the lesion and bonding affinity towards the biomarkers [86].

Third, limited toxicity and the absence of radioactivity further encourage the development of nanotechnology [87]. Taken together, the physical and biological advantages make nanoparticles attractive candidates for molecular imaging.

In recent times, emerging research of nanotechnology in the field of imaging of vulnerable plaque imaging has attracted attention [88]. Nanoparticles have been designed to target a wide range of hallmarks of vulnerable plaques, barely less than the radio-labeled platforms. Since the 2000s, given the optimistic results, the disagreement and interest remain focused on the most appropriate selection of signature for targeting [89]. In the following sections, we review the current advances in diagnostic imaging techniques using nanoparticles based on different characteristics of vulnerable plaques.

5.1. Imaging by targeting the thin fibrous cap

The thinning of the fibrous cap is one of the main hallmarks of a vulnerable plaque. Autopsy-based studies indicate that the rupture of plaque often occurs at the margin or shoulder spot of the cap thinner than 65 μm [90]. Some published reports also conclude that the thickness of cap reaching less than 200 μm is a red flag [91]. Based on the preliminary evaluation by T1-weighted imaging, gadolinium-based contrast agents further improve the efficiency of structural visualization of the atherosclerotic lesions [92]. Nevertheless, limited by the resolution, identification of the microstructures of the plaque by MRI is undesirable. The measurement of cap thickness remains challenging in clinical settings.

The integrity of fibrin is critical for the vulnerability of plaque in vivo [93]. Several authors have used nanotechnology to further assess the fibrin content in cap tissue based on which the nanoparticles targeting fibrin have been designed in animal and human studies. For example, Flacke et al. demonstrate the sensitivity of detection for a thin layer of fiber over the clot surface of plaque using paramagnetic nanoparticles targeting fibrin through an MRI scan [89]. In another study comprising 20 patients with carotid stenosis, a greater signal drop in asymptomatic cases suggests stability in vulnerability using ultra-small super--paramagnetic iron oxide [94]. What is more, gold nanoparticles, owing to their biocompatibility, modification ability, and superior optical properties, have been used to amplify the signal in MRI as ultrasmall metal-based contrast agents [95]. Jeong-Yeon et al. published an example of fibrin-targeting imaging using glycol-chitosan-coated gold nanoparticles for the detection of cerebrovascular thrombi, showing a signal enhancement after injection of nanoparticles [96]. Herein, these data suggest that the designed magnetic nanoparticles detected by MR can identify fibrous caps for the detection of vulnerable plaques.

Recruitment of massive macrophages in the plaque is another hallmark linked to fibrous cap thinning. Owing to its important role in the formation of plaques, along with the technical facility for binding, this has been favorable for researchers [97]. Years ago, nanoparticles are designed for targeting macrophages mainly by phagocytosis effect [98]. To reduce the non-specific interception by other immune organs, the use of nanoparticles designed to bind specific receptors on the cellular surface has received traction in the last five years [99]. Some recent and representative work emphasized on imaging vulnerability plaques are summarized in Table 2.

As mentioned earlier, MMP levels in vivo represent the enzymatic changes in the weak fibrous cap. Although the number of relative studies assessing MMP expression is unremarkable, some of them suggest that the nanotechnology platform can be used as a promising tool. For instance, Kiyuk et al. have constructed an MMP-targeting nanoparticle for a carotid plaque, wherein a sensor activated by MMP was tracked by fluorescence microscopy [115]. In addition, some proteins involved in the processing of MMP is also used as a biomarker. For example, a previous study suggests that gadolinium paramagnetic nanoparticles incorporating a binding peptide, targeting an inducer of MMP, EMMPRIN, qualifies for plaque evaluation [116]. The magnetic resonance sequences were allowed in the imaging when the signals in plaques significantly reduced (Fig. 4).

Given the association between the hallmark of collagen and vulnerable plaques, some research groups have established that nanoparticles targeting collagen are a vulnerable fiber in mice. For instance, a previous study on high-density lipoprotein nanoparticles reports a strong affinity for binding collagen. There is a significant increase in the MRI signal in the regression plaque [117] (Fig. 5A1, A2). Likewise, a new type of organic nanoparticle coating the platelet membrane also interacts with collagen [118]. Its live detection demonstrates its utility in MRI of atherosclerotic plaque. Alternatively, several studies suggest that the exposure of collagen IV facilitates nanoparticles to target the atherosclerosis plaques [119]. In a comparative study that evaluated different potential targets, nanoparticles conjugated by collagen IV-targeting peptides were found to enhance the image, though lower efficiency

Table 2
Summary of recently published studies on nanoparticles targeting macrophages in imaging of vulnerable plaques.

Target	Nanoparticles	Results	Years
Phagocytosis			
Phagocytosis	Ultrasmall superparamagnetic iron oxide	Reduction in standard signal intensity in T2WI MRI is associated with plaque stability	2020 [100]
Phagocytosis	Very small superparamagnetic iron oxide nanoparticles and Gd-BOPTA	Contrast agent based on Gd indicates arterial calcification and characterizes plaque vulnerability.	2020 [101]
Phagocytosis	Ultrasmall superparamagnetic iron oxide with rhodamine	T2 signal loss and spontaneous fluorescence appeared in the aortic plaque.	2019 [102]
Phagocytosis	Very small iron oxide particles using acids	Nanoparticles developed for MR were allowed for plaque identification	2015 [103]
Surface molecular of macrophages			
Scavenger receptors (SR-A)	Nanoparticles capsuling Fe_3O_4 and perfluoropentane	Nanoparticles show good imaging properties in ultrasound and MRI. Apoptosis of macrophages and disaggregation of platelets are observed (Fig. 3).	2021 [104]
SR-AI	Magnetic mesoporous silica nanoparticles	particles target and quantify macrophage enrichment in the plaque	2021 [105]
CD36	Hydrogel nanoparticles encapsulating Gd-DTPA	Ex vivo electron microscopy indicates atherosclerotic plaque associated macrophages targeted by nanoparticles.	2021 [106]
CD44	Single-dispersed iron oxide nanoparticles	An intelligent in vivo switch in T1-T2 enhancement modes shows that the vulnerable plaques exhibit	2021 [107]
SR-AI	Gadolinium-integrated gold nanoclusters	In vivo MR/fluorescence images demonstrated robust and prolonged contrast enhancement of signal.	2019 [108]
Osteopontin	Nanoparticles containing perfluorooctyl bromide and Cy5.5	Ultrasound and optical imaging reveal nanoparticles are accumulated in vivo.	2019 [109]
MARCO	Upconversion nanoparticles by conjugating MARCO antibody	High signal intensity on T1-weighted MR images are determined by 7.0T MRI.	2019 [110]
SR-A	Nanoparticles combined with the phase transitional material	Nanoparticles reduce the T2 signal in MRI scans and phase transition treatment leads to the apoptosis of macrophages.	2019 [111]
CD68	Fe-doped hollow silica nanoparticles	US/MRI platform indicates that the contrast agent is beneficial for identifying the macrophages in aorta.	2018 [112]
Osteopontin	An osteopontin specific MRI/optical dual-modality probe	MR displays T2 enhancement after injection.	2017 [113]
Osteopontin	Upconversion nanoparticles	The signals of vulnerability induced by lowered shear stress presented different signal intensities.	2017 [114]

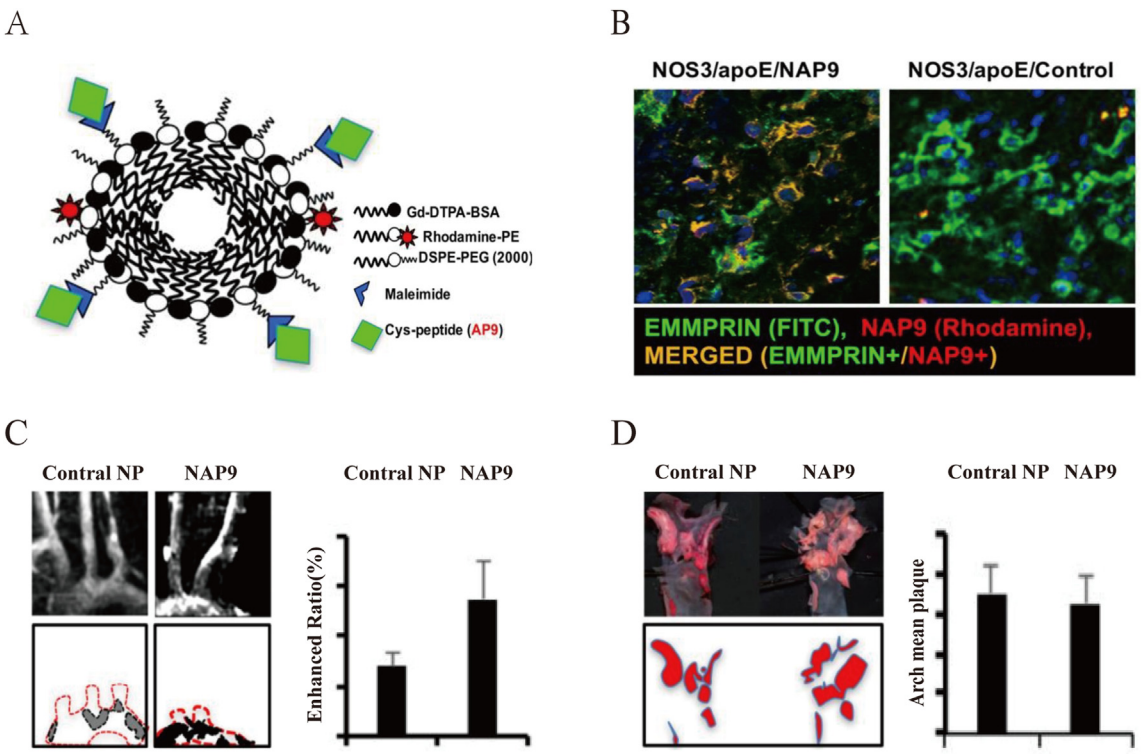

Fig. 4. An examples of nanoparticles functionalized for targeting matrix metalloproteinases for imaging vulnerable plaques. A) Scheme illustration of synthesis of nanoparticles with NAP9 peptides to visualize EMMPRIN. B) Confocal microscopy-based detection of EMMPRIN (green) and NAP9 (red). C) MRI images of gadolinium-enriched nanoparticles in the atherosclerotic aortic arch. D) Oil Red O staining in the atherosclerotic specimen. Reprinted with permission from ref. 116. Copyright 2018 Multidisciplinary Digital Publishing Institute.

was observed in the early stages of atherosclerosis [120]. Additional particulate studies of nanoparticles targeting collagen IV for drug delivering have been reported [121,122].

5.2. *Imaging by targeting necrotic core enlargement*

The large necrotic core is a morphological hallmark of a vulnerable plaque. The size and volume of the necrotic core are key predictors of prognosis [123]. Although there is no valid study that evaluates the role of nanotechnology for the assessment of the necrotic core, the MRI platform, widely used for nanoparticles, yields satisfactory images. This establishment is especially reliable for suspected blood vessels located in a certain position, such as the carotid artery, based on hypo-intense T2w images or CE-T1w images [124]. Recently, considerable efforts have been made to determine the threshold for defining a large necrotic core. According to a clinical study consisting of 120 carotid plaque subjects, the necrotic core with a volume larger than 40% was found to more likely rupture during the three-year follow-up [125]. In contrast, others suggest a volume greater than 10% of the necrotic core as a high-risk factor [126].

Additionally, intraplaque hemorrhage is emerging as another feature of necrotic core enlargement and vulnerable plaques [127]. Based on existing knowledge, MRI scans with standard coils and procedures can detect the existing intraplaque hemorrhage, the value of which has been determined by high-grade evidence [38]. The T1 weighted or hyper-T1 contrast weighted MRI procedure is performed depending on the oxidative state of hemoglobin [128,129]. Taken together, the current desire to examine novel applications of nanoparticles targeting large necrotic core or intraplaque hemorrhage is relatively low.

Annexin V representing apoptosis in the plaque, especially in the shoulder region of the fibrous cap, increases the vulnerability of plaque [130]. A high expression of annexin V is emerging as a hallmark for targeting. For instance, Burtea et al. have designed an ultrasmall superparamagnetic iron oxide nanoparticle targeting apoptosis in macrophages and show that it can localize to the vulnerable plaques [131]. This result has been confirmed in a similar study, wherein a hybrid nanoparticle targeting annexin V in macrophages has been constructed [132] (Fig. 6). Findings from a previous study on high-density lipoprotein mimicking nanoparticles support that stimulating apoptosis through the mitochondrial membrane potential facilitates the detection of vulnerable plaques [133]. Gold nanoparticles with enhanced targeting ability for annexin V have also been successfully synthesized to image vulnerable plaques [134].

Over the last decades, calcification in the vascular system is referred to as a significant gauge of fibrous cap rupture [135]. Mechanistically, the orientation, location, and size of spotty calcification are related to the rigid stress of the lesion [136]. However, there is still no reliable imaging method for a detailed evaluation of calcification due to the limited resolution of non-invasive instruments and the risk of invasive inspection [137]. Hence, several studies on nanoparticles targeting calcium or hydroxyapatite, a calcium phosphate mineral found in calcified vessels, have been evaluated. For example, several in vivo studies have highlighted novel nanoparticles functionalized with bisphosphonate-derivatizing. They can be used to visualize the osteogenic activity and provide a possible solution for the identification of micro-calcifications [138]. In another recent study with gold nanoparticles which allows for the evaluation of plaque calcification, the image is also found to be enhanced [139].

Neo-angiogenesis in the plaque contributes to its potential rupture. The present clinical evidence for neo-vascularization detection is typically based on the contrast-enhanced ultrasound method [140]. An ordinary MRI scan is not advantageous unless preceded by a specialized technique like dynamic contrast enhancement perfusion [55]. The nanoparticles targeting neo-vascularization have been energized by some authors. A study using rabbits, whereby they were injected with paramagnetic nanoparticles targeting αvβ3, a signature of neo-angiogenesis,

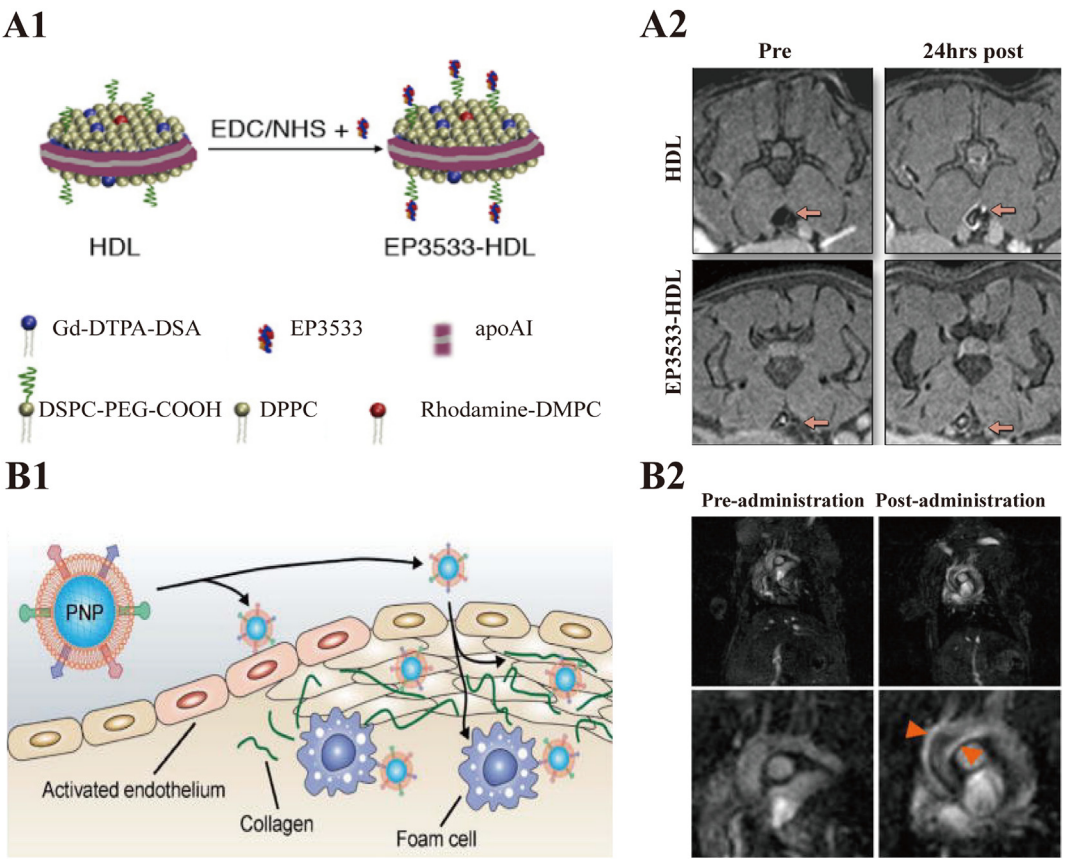

Fig. 5. Examples of nanoparticles functionalized for targeting collagen for imaging vulnerable plaques. A1) Scheme illustration of nanoparticles based on high-density lipoprotein functionalized with collagen-specific with peptides (EP3553). A2) MRI of abdominal aorta by injection of collagen-specific nanoparticles (EP3533). Reprinted with permission from ref. 117. Copyright 2013 American College of Cardiology Foundation. Published by Elsevier Inc. B1) Schematic illustration of platelet membrane-coated nanoparticles targeting collagen and multiple hallmarks. B2) MRI of ApoE KO mice after administration of nanoparticles (orange arrows: positive contrast in aorta). Reprinted with permission from ref. 118. Copyright 2018 American Chemical Society.

suggests an increased and heterogeneous distribution of positive signals along the longitudinal and transverse planes [43]. A recent study shows that the iron oxide nanoparticles conjugated with peptides that bind to αvβ3 are more efficient relative to those targeting collagen in the early stages of atherosclerosis [120] (Fig. 7). Thus, neo-angiogenesis is another potential biomarker that can be targeted using nanoparticle technology.

5.3. *Imaging by targeting the activated endothelium*

An important adhesion molecule that mediates leukocyte adhesion response, VCAM-1, is found to be overexpressed when the endothelium is activated in atherosclerosis. Thus, in numerous studies, VCAM-1 has been the target of nanoparticles. For example, Carmen et al. have evaluated the ultra-small superparamagnetic iron oxide nanoparticles conjugated to VCAM-1 and report that these can be effectively used to image the vulnerable plaques [131]. Likewise, in a previous study using liposomes conjugated with antibodies against cell adhesion molecules, the authors have detected atherosclerotic potentially vulnerable plaques in the early stage [141]. Interestingly, using plant viral nanoparticles to target VCAM-1, the findings indicate that the cargo raises the detection limit of atherosclerotic plaques [142] (Fig. 8).

6. The preclinical challenges to the application of nanoparticles

Over the past decades, great efforts have been made to promote the transformation of nanotechnology in clinical settings. However, the exciting findings using nanotechnology are just mainly staying at the preclinical stage for animal species. Only a few pioneering products have been approved by the FDA or other authorities after being evaluated for their safety in humans [143]. In addition, most of these pioneering products have focused on the diagnosis or treatment of tumors, and some for the treatment of patients with iron-deficient anemia [144,145]. While only a limited number of clinical trials for imaging atherosclerosis using nanotechnology have been underway, these suggest their safety and feasibility [146–149]. There are also some have been registered and are underway (such as NCT05032937).

There are many vascular similarities between humans and experimental animal, however, a huge gap may exist [150]. Thus, the necessity of determining the practical feasibility of nanotechnology through trials for imaging human plaque has emerged. The continuous discovery from these trials will aid the evolution of nanoparticle synthesis and imaging technologies. To date, several major challenges in clinical transformation remain unaddressed.

The first of them is the safety of nanoparticles for atherosclerotic vessels. For nanoparticles, the notion of toxicity has been initially investigated based on environmental exposure [151]. Some studies reveal the influence of various newly designed nanoparticles on the human body, but the inferences have not yet been fully elucidated [152]. In contrast to the nanoparticles used in cancer treatment, those targeting vascular structures need better biological adaptability, especially as their deposition can cause vascular inflammation [153]. Moreover, for clinical follow-up, there may arise a need for injecting the nanoparticles repeatedly in the same individual, which may cause a higher dose of deposition and serious complications. Thus, these newly designed nanoparticles must be strictly evaluated for toxicity. The solution to this challenge is contingent on engineering developments and innovations.

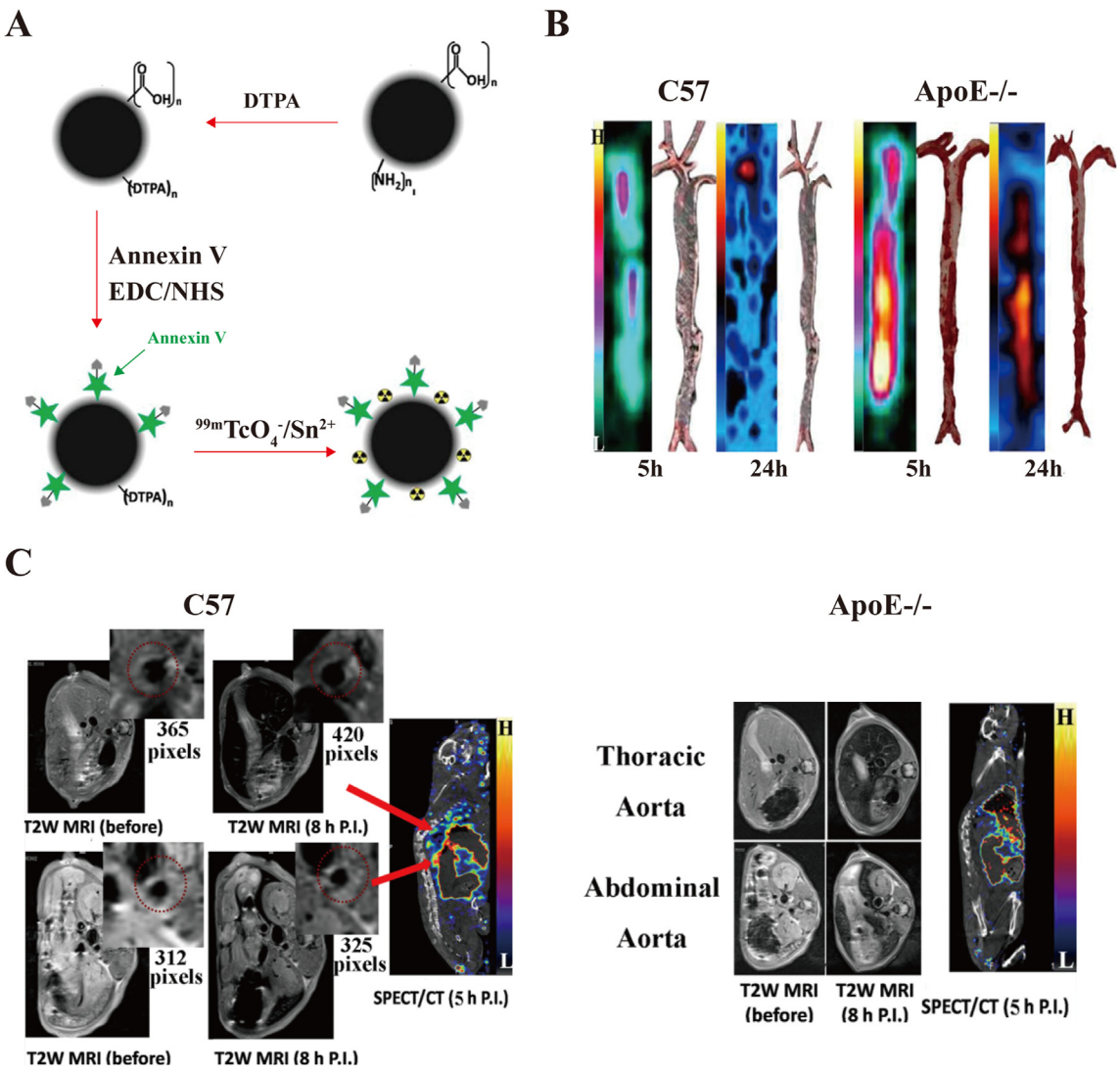

Fig. 6. A hybrid nanoparticle system verified using a single-photon-emission computed tomography/magnetic resonance imaging multimodal probe targeting annexin V. A) The protocols preparation of nanoparticles. B) The BSGI images have been confirmed by a corresponding Oil Red O staining in C57 and ApoE$^{-/-}$ mice. C) The images of nanoparticles targeting annexin V are seen in the aorta of ApoE−/− mice, but not in those of the C57 mice. Reprinted with permission from ref. 132. Copyright 2015 American Chemical Society.

The second challenge is to identify a more valuable hallmark for the vulnerable plaques for clinical decision-making. The majority of the current positive evidence for vulnerable plaques is based on structural imaging [154]. On the contrary, the results of animal experiments for identifying predictive molecular features have not been verified in long-term follow-up or human trials. In addition, researchers have to continuously discover new molecular targets in pursuit of novelty. Thus, there is no persuasive consensus on the best molecular features [155]. Additionally, owing to the complexity of the underlying mechanisms, it may be difficult to represent the overall state of plaques only based on a single molecular phenotype [156]. Therefore, biotech companies employing nanotechnology may not support a clinical trial without a solid evidence base. To solve this problem, as a starting point, studies focused on comparative efficacy are expected to provide novel insights. Furthermore, the nanoparticles targeting multiple properties warrant consideration [118](Fig. 5 B1, B2).

The third challenge is to acquire sophisticated equipment, which accommodates the contradiction between a wider screening range and a higher local resolution. Thus far, the spatial resolution of equipment based on nanotechnology is inadequate. As with all the other devices capable of molecular imaging, their expertise primarily deals with the imaging of large blood vessels, including the aorta and carotid arteries [157]. However, imaging the vessels smaller than the spatial resolution of cameras, like coronary arteries, poses difficulties, especially when they are in motion [158]. As for the MRI machines using nanoparticles, the largest benefits are proven convenience and penetration. However, the challenge of identifying the microvascular structure remains unaddressed, raising the need for improved equipment. In addition, combining other instruments with an improved local resolution, such as OCT, may also aid in overcoming this challenge [159].

Lastly, quantification and analysis of results from nanoparticle imaging tests pose another challenge. The heterogeneity in vulnerable plaque may exist, causing an inconsistent level of characteristic expression in individuals [160]. For example, different amounts of VCAM-1 can be expressed in stable plaque as well, resulting in the accumulation of nanoparticles and boosting the signal [161]. Thus, the threshold value defining these “positive results” are hardly unified depending on decentralized experimental designs. Meanwhile, imperfect properties of pharmacodynamics and pharmacokinetics may result in unexpected uptake by non-target tissues or clearance times in the target tissues, leading to over-interpretation and distrust in the conclusions [162]. Therefore, more preclinical studies, along with more sophisticated design, a larger

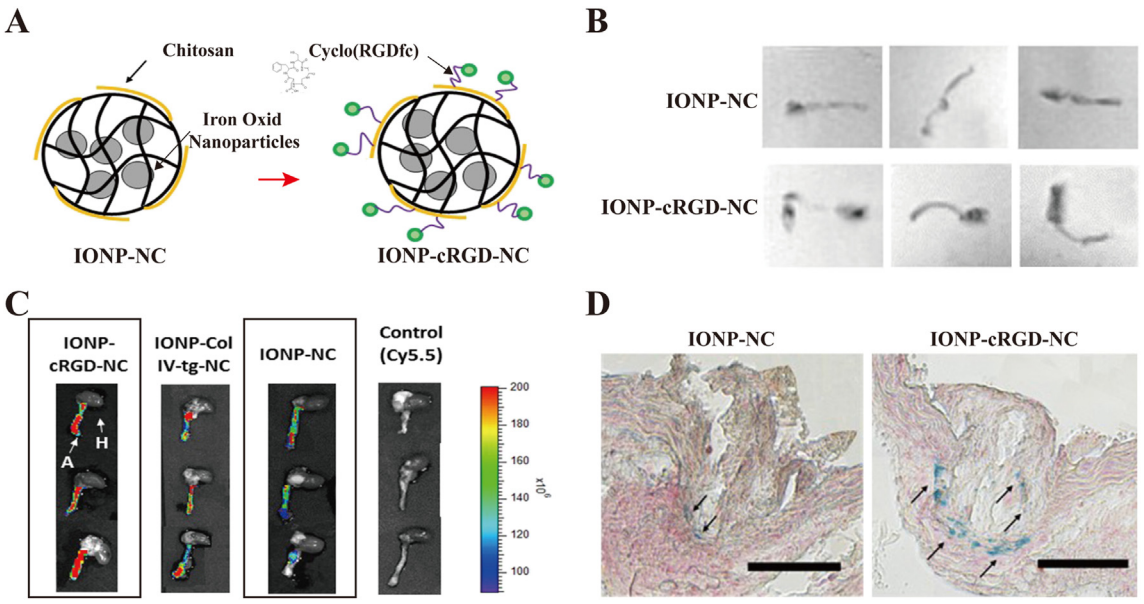

Fig. 7. An examples of nanoparticles functionalized for targeting neo-angiogenesis for imaging vulnerable plaques. A) Scheme illustration of nanoparticles of cRGD peptide to bind with the αvβ3 of the neo-vasculature. B) The fluorescence and C) MRI scan of aorta from apoE$^{-/-}$ mice injected with nanoparticles, IONP-cRGD-NC (targeting neo-angiogenesis), or IONP-NC(control). D) Atherosclerotic plaque staining with Prussian blue in apoE$^{-/-}$ mice. Black arrows indicate IONP nano-carrier. Reprinted with permission from ref. 120. Copyright 2017 Elsevier BV.

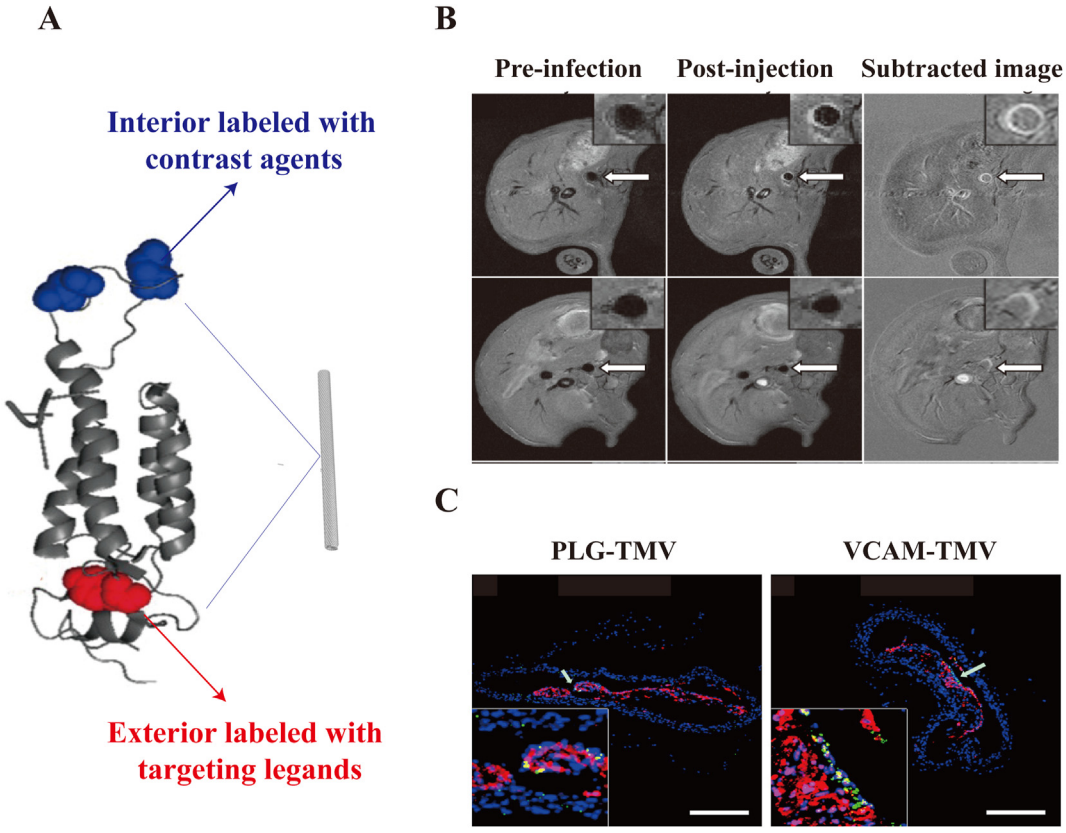

Fig. 8. An example of nanoparticles functionalized for targeting adhesion molecules for imaging vulnerable plaques. A) Scheme illustration of nanoparticle-based tobacco mosaic virus to target vascular cell adhesion molecule (VCAM-1). B) The MRI scans of the aorta wall in apoE$^{-/-}$ mice injected with nanoparticles targeting VCAM (1st line) and Gd ions control (2nd line). C) Representative confocal images from ApoE−/− mice injected with PEG-TMV (control) or VCAM-TMV; the particles are colored green. Reprinted with permission from ref. 142. Copyright 2014 American Chemical Society.

number of samples, and wider period coverage, are needed to understand these potential biases.

7. Conclusion and future directions

Atherosclerotic vulnerable plaques have more potential risks than stable plaques owing to their structural and molecular biology features. Nanotechnology offers a promising opportunity to identify the hallmarks representing the vulnerable plaque formation, thereby endowing them as qualified biological contrast agents. Considering the adaptability and limitation of different platforms, we believe that MRI enhanced by nanoparticle contrast is the most practical and comprehensive choice to date. Although many positive results in support have been demonstrated in animal studies, the evidence remains insufficient for the transformation of nanotechnology for human use. For example, several studies highlighted in this review do not point out their disadvantages or specify the accuracy. Moreover, no valid data are reported in human studies with sufficiently large sample size. Therefore, more studies are needed to examine the limitation of these types of biomaterials, their advanced nature, the terms for safety, biological targets, higher-resolution equipment, and quantitative systems among others. Major efforts are anticipated in the pharmaceutical, bioengineering, pathophysiology, and clinical settings.

Future clinical studies are also needed to elucidate their adaptability in humans. For example, the predictive value of nanoparticles for plaque rupture needs to be determined by prospective clinical trials along with a follow-up. A comprehensive scoring system, similar to coronary scoring, that considers multiple hallmarks or risk factors should be developed to improve diagnostic effectiveness [163]. Another potential direction is to evaluate hybrid imaging methods PET/MR to minimize the limitations of the equipment. Furthermore, multifunctional nanoparticles that enable the integration of diagnosis and treatment may expand their scope for clinical applications [164].

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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