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Review

Magnetic iron oxide nanoparticles as novel and efficient tools for atherosclerosis diagnosis

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ABSTRACT

Cardiovascular complications derivate from atherosclerosis are the main cause of death in western world. An early detection of vulnerable atherosclerotic plaques is primordial for a better care of patients suffering the pathology. In this context nanotechnology has emerged as a promising tool to achieve this goal. Nanoparticles based on magnetic iron oxide (MNPs) have been extensively studied in cardiovascular diseases diagnosis, as well as in the treatment and diagnostic of other pathologies. The present review aims to describe and analyze the most current literature regarding to this topic, offering the level of detail required to reproduce the experimental tasks providing a critical input of the latest available reports. The current diagnostic features are presented and compared, highlighting their advantages and disadvantages. Information on novel technology intended to this purpose is also recompiled and in deep analyzed. Special emphasis is placed in magnetic nanotechnology, remarking the possibility to assess selective and multifunctional systems to the early detection of artherosclerotic pathologies.

Finally, in view of the state of the art, the future perspectives about the trends on MNPs in artherosclerorsis diagnostic and treatment have also been addressed.

Contents

1. Introduction

Atherosclerosis is a chronic inflammatory disease, characterized by the formation of a lipid-rich plaque inside the arteries. The formation of atherosclerotic plaques occurs in curvatures and

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branch points of arteries. This situation causes arterial wall thickness, limiting the flow blood to the organs. Despite the advances in the prevention and therapy of cardiovascular pathologies, they are still the first cause of death in the western world.

In general terms; two types of atherosclerotic plaques may be found: one known as stable plaque and other called vulnerable plaque. The former is usually rich in extracellular matrix and smooth muscle cells whereas the vulnerable plaques are rich in macrophages, other inflammatory cells and exhibit a fibrous cap. While stable plaques can be present without causing any damage for years, vulnerable plaques are prone to rupture and release thrombus into circulation causing myocardial infarction and stroke [1,2]. For that reason, an early detection of unstable plaques is primordial in the prevention of these dramatic cardiovascular events.

Several dealings are involved in the initiation and progress of the disease [3]. Initially, the excess of low density lipoprotein (LDL) in the circulation starts to accumulate in the arterial lumen wall, where the lipoproteins suffer modifications such as oxidation, cleavage and aggregation. This process causes a chronic injury to the endothelial cells, activating the inflammatory process through the expression of surface adhesion molecules such as VCAM-1 and ICAM-1, which may recognize monocytes and T lymphocytes. Monocytes differentiate into macrophages and take up the ox-LDL generating foam cells charged with cholesterol. When foam cells died, they release their lipid content and tissue factors causing the formation of a pro-thrombotic necrotic core, which is the key component of unstable plaques [4–6]. Scheme 1 illustrates and summarizes the major events involved in plaque destabilization.

Nowadays, the development of nanotechnology at the health service has opened novel perspectives in relation to the treatment and diagnosis of several diseases [7–9]. The possibility of designing nanoparticles with specific ligands or functional groups, able to preferentially bind and recognize one or more compounds in unstable plaques, appears as an invaluable tool in the early diagnosis of atherosclerosis. The current research trends cover multiple nanosized systems intended as contrast agents for cardiovascular imaging; such as fluorescent, radioactive, paramagnetic, superparamagnetic and multimodal, among others [10].

In this context, the present review is focused on the use of magnetic iron oxide nanoparticles as improved contrast agents for the detection of unstable plaques by Magnetic Resonance Imaging (MRI) as a way to attain the early diagnosis of atherosclerosis.

It is well known that the articles in open literature reporting different aspects and applications of MNPs are abundant [11–13]. In spite of this, the published reports regarding to magnetic nanoparticles for the detection and treatment of atherosclerosis are significantly lower [14–16]. Besides, the present review involves different approach in several points. In first place, the discussion will be restricted to the use of iron oxide magnetic nanoparticles as contrast agents for the mentioned pathology. The aim is to discuss on the most suitable modifications/functionalization for conferring specificity to the magnetic nanoparticles for atherosclerotic plaque detection. Secondly, the importance and the advances in the synthesis of dual modal magnetic nanoparticles will also be addressed.

Hence, this contribution proposes a different view regarding to a very actual topic that has not been addressed from this point of view in the actual literature, at least to the best of these authors knowledge.

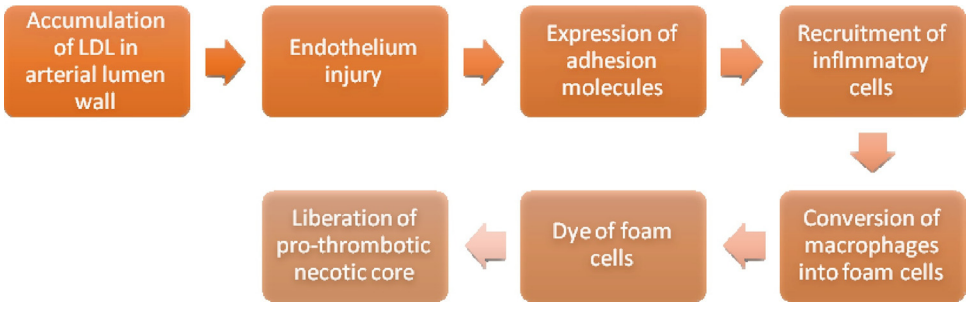
2. General aspects of imaging diagnosis, differences between them

In general terms, imaging techniques may be classified in morphological, functional and molecular imaging [17]. While the former shows the final effect of molecular alterations, functional and molecular imaging provide biological information of a disease in a non-invasive way [18–20]. These last techniques have been analyzed in great detail in the context of this Review, because MNPs may be suitable to improve the quality of the image acquired by these techniques.

Molecular imaging is recognized as a powerful technique to detect diseases in the early stages. It is also able to recognize the pathway of a disease monitoring the response to therapy [21,22]. This technique requires two important elements: molecular probes or imaging agents and a hardware to control the probes. Molecular/functional imaging modalities include positron emission tomography (PET) [23], single-photon emission computed tomography (SPECT) [24], computed tomography (CT) [25], fluorescence molecular tomography (FMT) [26], photoacustic tomography (PAT) [27,28] and magnetic resonance imaging (MRI) [29].

Each imaging modality exhibits advantages and disadvantages. A summary of those advantages and disadvantages as a function of each technique is shown in Table 1. For example, PET and SPECT have excellent sensitivity and elevated tissue penetration but low resolution whereas MRI provides high resolution anatomical images and satisfactory tissue contrast. However, it displays low sensitivity and poor tissue penetration. On the other hand, the use of CT may provide high resolution 3D but weak contrast soft-tissue images. This fact justifies the need of designing multi-modal imagining systems as an improved option to obtain molecular images.

The advance of nanotechnology has generated novel kinds of materials highly attractive in the area of molecular imaging. The possibility to design nanomaterials with well-defined and controlled physical and chemical properties represents a great benefit over the traditional contrast agents. Besides, the most



Scheme 1. Principal events involved in the formation of an atherosclerotic unstable plaque.