Pharmacological Reports 67 (2015) 751–755

Contents lists available at ScienceDirect

Pharmacological Reports

journal homepage: www.elsevier.com/locate/pharep

Review article

Nanoparticles in endothelial theranostics

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ARTICLE INFO

Article history:
Received 9 February 2015
Received in revised form 18 May 2015
Accepted 20 May 2015
Available online 4 June 2015

Keywords:
Nanoparticles
Theranostics
Cardiovascular diseases
Atherosclerosis
Thrombosis

ABSTRACT

The paper presents the recent advances in the development and studies of multifunctional nanoparticles which can be used to prevent/cure the cardiovascular diseases by detecting, treating and monitoring the early stages of atherosclerotic and thrombotic changes in endothelium.

Contents

Introduction

Development of nanotechnology affected many areas of human activity, including medicine. Application of nanotechnology in medicine resulted in the advent of nanomedicine which revolutionized both diagnostics and therapy. Nanomedicine utilizes materials and devices of nanometric dimensions, often prepared *via* operations carried out on the molecular level. The properties of such systems are quite different than these characteristics of the macroscopic ones and can be adjusted to the specific needs [1]. Nanoparticles are the most popular nanostructures utilized in nanomedicine. They have tunable electronic, optical, magnetic and biological properties. Nanoparticles can be manufactured as the objects of various chemical composition, surface characteristics, size and shape. They can be prepared from various materials such as metals, metal oxides, silica, natural and synthetic polymers, carbon, lipids and biomolecules. They can exist as hollow, porous or solid structures of different morphologies such as spheres, cylinders, tubes or platelets [2]. Nanoparticles can be loaded with various substances, *e.g.* drug molecules. These objects have large surface area per unit of volume what is particularly important for their interactions with other objects/(bio)surfaces. The nanoparticle surface can be tailor-made or designed to address specific needs. The modification can involve attaching the specific ligands/antibodies/peptides allowing active drug delivery to the targeted tissue as well as the prolonged circulation in the blood, thus

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http://dx.doi.org/10.1016/j.pharep.2015.05.018
1734-1140/

increasing the probability of the passive drug delivery, *e.g.* by the Enhanced Permeability and Retention (EPR) effect in the abnormal vasculature of the cancer tissue. Recently, there has been a considerable effort to use the same nanoparticles for multimodal diagnosis and therapy, which include targeted drug delivery and its sustained and/or controlled release (Fig. 1).

Such integration of both of these medical procedures was named "theranostics". The most often used nano-sized materials for theranostic purposes include: polymeric, lipid-based or metal oxide nanoparticles, dendrimers and cage proteins [3–6]. These nanoparticles are attractive for the theranostic applications, mainly because of their ability to be located in pathological lesions rather than in normal tissues, particularly in the case of cancer or in dysfunctional endothelium [7,8]. It is believed that theranostic approach can improve the outcome and increase the safety of medical procedures. It should allow identification and treatment of the diseases at their earliest stage when the chances for patient's recovery are relatively high and to monitor/correct the treatment. In that regard, theranostics can be very helpful in the development of personalized medicine which replaces the standard diagnostic and therapeutic strategies by individualized approach taking into account the inter-individual variability in therapeutic response. Recently, there has been a growing interest in the potential application of the personalized treatment for widely spread and difficult to cure degenerative diseases such as cancer, neurodegenerative disorders and cardiovascular diseases. To develop that person-oriented and disease-oriented theranostic treatment for all these diseases, one has to design and synthesize the multifunctional nanoparticles and study their interactions with endothelium, the thin continuous layer of cells lining the luminal surface of blood vessels which is the interface between circulating blood and the vessel wall. Thus, endothelium is the first contact point for nanoparticles, especially when introduced *via* injection, but also serves as a barrier protecting extravascular sites. It is a main target in the treatment of inflammation, neurological, cardiovascular (ischemia, thrombosis and stroke), pulmonary and oncological diseases. In the current paper, we discuss the recent advances in nanotheranostics of early stages of cardiovascular diseases.

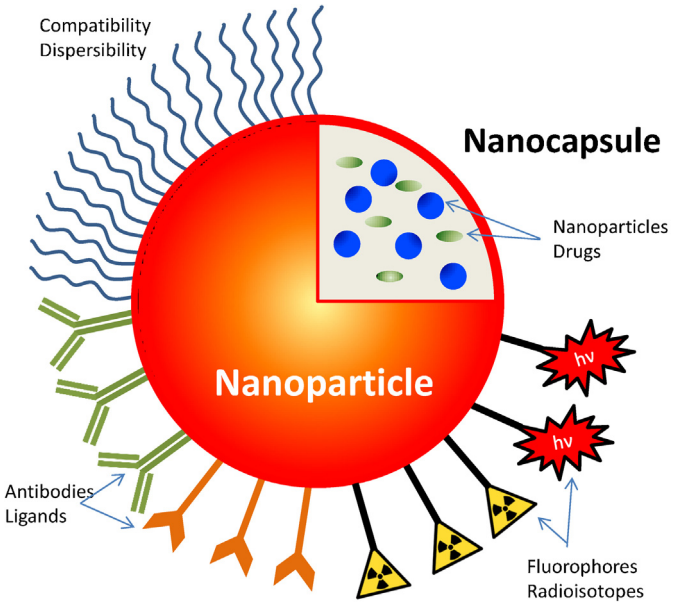

Fig. 1. Schematic structure of nanoparticles/nanocapsules for biomedical applications.

Nanotheranostic strategies in cardiovascular diseases

Cardiovascular diseases (CVD) are the leading cause of morbidity/mortality worldwide. Each year CVD account for over 4 million deaths in Europe and over 1.9 million deaths in the EU. It is predicted that in 2030, the number of CVD-related deaths will increase to 23.6 million world-wide [9]. There is a number of identified causes, both biological and environmental, for the development of these diseases. Although the medical procedures were considerably improved in the last decades, their general therapeutic results are not satisfactory. That is mostly due to the fact that the therapy is implemented when the disease is already advanced, or quite often even after it has been manifested in cardiovascular events (such as myocardial infarction (MI) or stroke). It should be also noted that some patients do not respond positively to the currently used treatment. Thus, there is a need for the sensitive and possibly noninvasive procedures allowing detection of these diseases at the early stage and for novel drugs/therapeutic methods [10].

Atherosclerosis

As the majority of CVD start from the atherosclerosis, which has been recognized as an inflammatory-type disease, the tools for its detection and inhibition are necessary [11,12]. Currently, atherosclerosis is diagnosed at the advanced stages by direct measurements of degree of stenosis, or indirectly, by the determination of the effect of arterial stenosis on organ perfusion. However, even at the early stages of atherosclerosis, there are considerable changes in endothelium structure and chemistry–the gaps between endothelial cells are formed leading to increased endothelial permeability and the level of the expressed adhesion molecules is growing. Those changes induce accumulation of low-density lipoproteins and activated macrophages followed by adhesion of extracellular proteinases, apoptotic cells and free radicals, resulting in building of atherosclerosis plaques. The progression of the plaque formation induces the hypoxia-driven angiogenesis leading to the formation of new blood vessels. In the final stage of atherosclerosis, the components of plaques are exposed to blood and induce thrombosis manifested by the clinical symptoms, such as MI or stroke. Surprisingly, there have been only very few studies on atherosclerosis detection based on monitoring the level of inflammatory biomarkers. There is, however, much more activity on improvement of the sensitivity and efficiency of various molecular imaging techniques, such as magnetic resonance imaging (MRI), optical fluorescence imaging (OFI) or positron emission tomography (PET). Recent progress in MRI was possible due to the application of properly designed and synthesized contrast agents. There are so-called positive and negative MRI contrast agents. The former ones reduce proton longitudinal relaxation time, T1, providing the positive contrast (bright signal), while the latter ones are T2 agents that shorten proton transverse relaxation time causing negative contrast (dark signal) [13]. Positive contrast agents are typically paramagnetic compounds, usually gadolinium complexes or manganese ions, while superparamagnetic materials, mainly these based on iron oxide nanoparticles, act as the negative contrasts [14,15]. It is believed that dual-mode T1–T2 contrast agents, combining the advantages of positive and negative contrasts, may improve diagnosis [16,17].

Nanostructural materials were shown to have clear advantages over conventional MRI agents. Nanometer dimensions of these materials have considerable impact on magnetic properties and ability to operate on cellular level [18–21]. Originally, single functional superparamagnetic iron oxide nanoparticles (SPION) with size of 100–180 nm and ultrasmall superparamagnetic iron