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Review

Nanomaterial-Based Drug Targeted Therapy for Cardiovascular Diseases: Ischemic Heart Failure and Atherosclerosis

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Abstract: Cardiovascular diseases (CVDs) represent the most important epidemic of our century, with more than 37 million patients globally. Furthermore, CVDs are associated with high morbidity and mortality, and also increased hospitalization rates and poor quality of life. Out of the plethora of conditions that can lead to CVDs, atherosclerosis and ischemic heart disease are responsible for more than 2/3 of the cases that end in severe heart failure and finally death. Current therapy strategies for CVDs focus mostly on symptomatic benefits and have a moderate impact on the underlying physiopathological mechanisms. Modern therapies try to approach different physiopathological pathways such as reduction of inflammation, macrophage regulation, inhibition of apoptosis, stem-cell differentiation and cellular regeneration. Recent technological advances make possible the development of several nanoparticles used not only for the diagnosis of cardiovascular diseases, but also for targeted drug delivery. Due to their high specificity, nanocarriers can deliver molecules with poor pharmacokinetics and dynamics such as: peptides, proteins, polynucleotides, genes and even stem cells. In this review we focused on the applications of nanoparticles in the diagnosis and treatment of ischemic heart failure and atherosclerosis.

Keywords: nanoparticles; cardiovascular disease; targeted therapy; atherosclerosis

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1. Introduction

Nanotechnology focuses on atomic and molecular structures with dimensions of 0.1–100 nm. The resulting nanomaterials exhibit distinct mechanical, electrical, thermal, magnetic and imaging features that facilitate novel and unique applications in different branches of science, such as nanomedicine, nanobiology and nanobiotechnology. In the field of medicine, nanoparticles (NPs) have been used to improve imaging techniques in very early stages of the disease, to access different sites (e.g., crossing the blood-brain barrier) and deliver different therapeutic agents to target cells (e.g., targeting only cancer cells without interacting with the normal tissue) [1]. Furthermore, nanomaterials are employed extensively in the field of regenerative medicine to replace damaged tissue [2]. In cardiovascular diseases (CVDs), nanotechnologies have four main applications: diagnostics, molecular imaging, targeted drug delivery, tissue regeneration and engineering. This is due to the fact that nanomolecules act as carriers facilitating controlled release of imaging and diagnostic agents at the site of the cardiac injury [3].

CVDs are one of the most important global epidemics of the 21st century, with an estimated prevalence of more than 37 million patients globally. Furthermore, CVDs have a worldwide distribution with high mortality and hospitalization rates being associated with a poor quality of life for the patients and high costs for healthcare systems [4,5]. Out of the plethora of conditions that can lead to CVDs, atherosclerosis and ischemic heart disease are responsible for more than 2/3 of the cases progressing to severe heart failure (HF) and finally death. The continuous increase of ischemic HF incidence in the last century can probably be attributed to the aging population, the increase of sedentarism, poor nutrition and smoking. Accumulating evidence from cohort studies and randomized clinical trials (RCTs) has brought novel insight regarding prevention and treatment for HF, and the absolute survival rate in the past 30 years has increased 9%. Furthering our understanding of this condition with its molecular and genetic pathways can make this percentage even higher [6]. The main physiopathological feature of ischemic heart failure is ventricular remodeling, and it consists of myocyte hypertrophy with loss of myofibrils and abnormal intracellular matrix, myocardial fibrosis with excessive accumulation of extracellular matrix components, and changes in the collagen fibers proportions, inflammation and activation of the inflammatory pathways, mitochondrial disfunction and finally apoptosis and autophagy [7].

Current trends of HF pharmacological treatment focus on the adrenergic and renin–angiotensin–aldosterone systems (RAAS), which are responsible for the regulation of vasoconstriction and fluid retention. Agents that induce RAAS inhibition (ACE inhibitors, angiotensin 2 receptor blockers and aldosterone antagonists) were proven in multiple RCTs to promote cardiac remodeling and reduce HF symptomatology, morbidity and mortality. Activation of the sympathetic nervous system secondary to reduced cardiac output leads to increase total peripheral resistance, activation of beta-adrenergic receptors increasing wall tension, oxygen consumption and myocyte necrosis [5]. Other peptides such as natriuretic peptides, bradykinin, substance P and adrenomedullin promote diuresis, natriuresis, vasodilation and inhibit the adrenergic system. Attempts to administer exogenous natriuretic peptides have not shown any effectiveness in HF therapy, especially due to their increased degradation. However, inhibiting neprilysin (a catalyzer of natriuretic peptide degradation) was proven to decrease HF hospitalization rates and mortality [4,8]. Another target for HF therapy is represented by the SGLT2 inhibition, which regulates renal sodium absorption, renin secretion, a catabolic state with lower insulin and higher glucagon levels, and has favorable effects on myocardial metabolism [8,9].

In contrast, modern therapeutical approaches try to focus on promoting cardiac regeneration through different mechanisms such as: reprogramming of cardiac fibroblasts into contractile cells, cardiomyocyte proliferation stimulation, gene and cell-based therapies [10]. The main challenges of these therapies arise from the specific pathophysiology of HF and result from the ability of the delivering agent to identify, target and deliver molecules or cells at the level of the damaged myocardium. Furthermore, in cases of cell therapy it is vital to also facilitate retention and engraftment at the targeted area, together with cell monitoring over the course of treatment. Most of these challenges could be surpassed by using nanoparticles as delivery systems.

2. Nanotechnologies and Diagnostic of Ischemic Heart Disease

One of the main staples of ischemic heart disease and HF successful management is early detection, which enables administration of proper treatment, improving the prognostic, quality of life and survival of patients. Current means of diagnosis are based on a cumulus of clinical signs, assessment of different heart-specific biomarkers and imaging modalities. However, the onset of clinical signs and pathological imaging findings manifest later in the evolution of the disease, while detection of biomarkers in the human plasma and conventional imaging techniques have limited sensitivity and specificity. In this context, nanotechnologies have been employed in order to enhance the detection and description of physiopathological mechanisms of cardiovascular diseases. These mecha-

nisms are atherosclerosis, thrombus formation and localization, myocardial infarction (MI), and postinfarction remodeling, angiogenesis and myocyte apoptosis [11].

Atherosclerosis is responsible for the development of heart failure directly in the context of ischemic heart disease and indirectly through hypertension, peripheral vascular disease and through promoting other comorbidities such as stroke and renal injury. Unstable atherosclerotic plaques are responsible for the majority of cases of myocardial infarction and sudden cardiac death. Current imaging techniques such as intravascular optical coherence tomography (OCT) can detect vulnerable plaques based on histopathological structure [12]. However, in order to better evaluate the severity of atherosclerotic plaques, a molecular analysis is necessary. Concentration of macrophages and their activity at the level of atherosclerotic plaque were shown to be an attractive indicator for plaque instability [13]. In this regard, nanoprobes composed of dextrinated and diethylenetriamine pentaacetate (DTPA) modified magnetofluorescent 20 nm nanoparticles have been used to target macrophages expressing CD68 at the level of atherosclerotic plaques. After coating this nanoprobe with ^{64}Cu, the accumulation of the probe at the level of atherosclerotic arteries of model apoE$^{-/-}$ mice was demonstrated through PET/CT and in vivo MRI [14]. In another study, fluorescent magnetic nanoparticles conjugates were used to target vascular adhesion molecule-1 (VCAM-1) expressed by unstable plaques, and the accumulation of the nanoparticles was confirmed by MRI [15]. There are also studies that use intravascular photoacoustic (IVPA) imaging based on administration of silica-coated gold nanorods (SiO2AuNR), which are thermally stable nanosensors, thus enabling temperature mapping of the plaque's activity and molecular composition. IVPA can be used in conjunction with intravascular ultrasound (IVUS) to evaluate both the morphology and the functionality of the plaque [16]. More information about pathological mechanisms involving atherosclerosis and NPs targeted therapies will be described later in this paper.

Thrombosis is usually a consequence of plaque rupture and is the underlying cause of clinical manifestations such as myocardial infarction or stroke. Furthermore, thrombus formation is encountered in other cardiovascular pathologies such as atrial fibrillation, ventricular aneurysm and venous embolism (deep vein thrombosis and pulmonary embolism). In order to identify thrombi, researchers tried to use different molecular targets such as fibrin, cell-adhesion proteins and activated platelets. For example, the pentapeptide Cys-Arg-Glu-Lys-Ala has a high specificity for fibrinogen/fibrin complexes and when conjugated with a dye-conjugated H_2O_2-scavenging polymer it targets newly formed thrombi [17]. Other studies have focused on P-selectin, a cell-adhesion protein expressed on activated platelets, which can be targeted by gadolinium-targeted paramagnetic or iron oxide nanoparticles, which enhance the MR imaging of microthrombi [18,19]. In addition to identifying the location of the thrombus, MRI together with florescence imaging can be used to further evaluate the severity of myocardial infarction. MRI is an ideal imaging technique used for the identification of tissue scaring and myocardial contraction, while fluorescence imaging can assess the biological processes at the level of the ischemic myocytes. Magneto-fluorescent nanoprobes such as cross-linked iron oxide (CLIO)-Cy5.5 are accumulated in the macrophages at the level of the myocardial infarction [20]. Using them as an MRI enhancement agent may lead to further understanding of the role of cardiac macrophage mediated inflammation, encountered in postinfarction cardiac remodeling. CLIO-Cy5.5 can also be conjugated with annexin V in order to detect and possibly stabilize early apoptotic processes in ischemic heart diseases [21,22].

In fact, most of the aforementioned nanomolecules can be also used to act as medication carriers to the targeted cells. Nanotheranostics (therapy and diagnostics) is characterized by 3 stages. Stage 1 implies the nanoparticle-based diagnosis of the disease and the evaluation of conventional treatment efficiency. In stage 2, nanomolecules are used for therapy, and in stage 3, nanoparticle-based imaging is used to evaluate the efficacy of nanotherapy [23]. Nanoparticles used in the diagnosis and imaging of cardiovascular diseases are summarized in Table 1.

Table 1. Nanoparticles used in cardiovascular imaging and diagnosis.

Nanoparticle	Molecular Mechanism	Imaging Technique
Dextrinated and DTPA modified magnetofluorescent [14]	• target macrophages expressing CD68 at the level of atherosclerotic plaques	• PET/CT and MRI of unstable atherosclerotic plaques
CLIO-Cy5.5 fluorescent magnetic nanoparticles conjugated with VHSPNKK polypeptide [15]	• target vascular adhesion molecule-1 (VCAM-1) expressed by unstable plaques	• MRI of unstable atherosclerotic plaques
CLIO-Cy5.5 conjugated with annexin V [21]	• detecting apoptotic heart cells	• MRI in ischemic heart disease and cardiomyopathies
Paramagnetic or iron oxide nanoparticles	• P-selectin on activated platelets	• MRI detection of thrombosis
AuNPs coated with collagen binding adhesion protein 35 [24]	• myocardial scar tissue	• alternative to iodinated contrast in CT imaging
Ferumoxytol—paramagnetic iron oxide nanoparticle [25]	• uptake at the level of activated macrophages in the ischemic myocardium	• MRI in ischemic heart disease
Silica-coated gold nanorods (SiO2AuNR) [16]	• detection of activated macrophages in unstable atherosclerotic plaques	• intravascular photoacoustic (IVPA) temperature mapping of the plaque's activity

3. Nanotechnologies and Therapy of Ischemic Heart Disease

Nanoparticles represent an ideal drug and molecule carrier as they are designed to elude the host's immune system, have an acceptable biodegradability, biocompatibility, and have the ability to target a specific site. Furthermore, due to the size of these molecules they can pass through the cell membrane and target desired cellular components. Some of the most studied nanoparticles in cardiovascular diseases are liposomes, dendrimers, micelles, polymeric and inorganic nanocarriers [26]. The treatment of ischemic heart disease consists of two main constituents. The first one is the treatment of the occluded vessels, while the second one consists of facilitating cardiomyocyte survival and regeneration, inhibition of inflammation and macrophage activation.

As mentioned before, nanoparticles can be used to target coagulation molecules or platelet adhesion in newly formed thrombi responsible for myocardial infarction. For example, a controlled release and thrombolytic activity of tissue-type plasminogen activator (tPA) and successful recanalization in swine MI models was attained through nanoparticles containing (tPA) coupled to von Willebrand factor [27]. Similarly, magnetic nanoparticles conjugated with urokinasis were directed for thrombolysis by a magnetic field at the site of the thrombus in an experimental mouse model [28].

In patients receiving a stent after an ischemic event, the risk of stent restenosis remains an important factor for the efficiency of the treatment. Nanocarriers that facilitate the retention of antiproliferative drugs at the level of the lesion of the endothelial tissue have been proposed as a prophylactic measure for stent restenosis. Lipid-based nanoparticles containing different classes of drugs such as bisphosphonate or prednisolone have been shown to reduce neointimal growth in atherosclerotic experimental models implanted with bare metal stents. Other polymeric-based nanoparticles such as polylactic-coglycolic acid (PLGA) nanoparticles were loaded with paclitaxel or sirolimus similar to drug eluting stent with acceptable results [29]. In 2007, the results of the systemic nanoparticle paclitaxel (nab-paclitaxel) for in-stent restenosis I (SNAPISTI) trial were reported, revealing that nab-paclitaxel doses under 70 mg/m^2 may be used to prevent stent restenosis [30]. Drug-eluting stents (DES) have had good results in preventing stent restenosis when compared to bare metal stents. However, DES inhibit the proliferation of the endothelial layer of the vessels, leading to an increased risk of thrombosis requiring long-term antithrombotic therapy. As a response to these issues, experimental studies have proposed various techniques to generate nanopatterns that promote proper endothelization on the surface of

titanium stents [31]. In addition, nanoparticle-eluting stents have been produced using nanomolecules, promoting endothelization with a satisfactory internalization into the smooth vascular muscle cells [32].

During ischemia, the tissue enters an acidotic state that results in releasing intracellular content and production of reactive oxygen species (ROS). H_2O_2 is the most abundant form of ROS, and its production is associated with proinflammatory cytokine release, myocytes apoptosis and the development of ischemic heart disease [33]. To reduce the effects of H_2O_2, nanoparticles linked by peroxalate bonds and containing antioxidant molecules can be delivered to the ischemic area. The peroxalate bonds are cleaved by excess H_2O_2 and thus the antioxidant molecules are released at the site of the oxidative stress [33]. Superoxide dismutase 1 (SOD1, Cu/Zn SOD) is an enzyme responsible for the degradation of ROS, and its overexpression has been shown to have a protective effect in experimental models of myocardial infarction [34]. Polyketal particles were designed to carry SOD1 and the use of these nanoparticles has been proven to improve cardiac function in myocardial infarction mice sustained by echocardiographic measurements [34].

Inorganic nanoparticles are composed of an inorganic core surrounded by an organic/inorganic shell being designed to avoid the host's immune system and thus increase biocompatibility. They are very well suited for theranostic purposes as the inorganic component can be used to enhance imaging techniques such as CT and MRI. Gold nanoparticles (AuNPs) are widely used because they are easily synthetized, they present low toxicity and immunogenicity, and have good stability. Due to these beneficial properties, AuNPs have been conjugated with drugs that are already used in clinical practice, such as levosimendan and beta-blockers. In an animal model of doxorubicin-induced HF, these aggregates showed significant cardio-protective effects [35]. Au NPs that accumulate in the ischemic heart tissue have been used to deliver and influence exogenous growth factors resulting in a 1.7-fold increase of blood perfusion at that level [23].

In the past decade, increasing evidence has shown that microRNAs (endogenous, conserved, single-stranded, non-coding RNAs of 21–25 nucleotides in length) have an important role in angiogenesis, apoptosis, cell growth, differentiation, cardiac cell contractility, control of lipid metabolism and plaque formation [36]. Among their multiple influences on cardiovascular and metabolism homeostasis, many experimental studies have shown that microRNAs serve as significant regulators and fine tuners of a variety of pathophysiological cellular effects and molecular signaling pathways involved in development of atherosclerosis [37]. AuNPs can be coupled with gene-regulatory molecules such as microRNA 155, increasing the expression of anti-inflammatory type 2 macrophages that mitigate local inflammation and myocytes apoptosis [38]. Albumin-polyvinyl alcohol-AuNPs nanofibrous scaffolds have also been shown to facilitate cardiogenic differentiation of mesenchymal stem cells [35,39]. Finally, AuNPs coated with collagen binding adhesion protein 35 can also be used as an alternative to iodinate contrast for the CT imaging detection of myocardial infarction [24].

Other inorganic NPs with excellent theranostic properties are iron oxide NPs (SPION). Due to their superparamagnetic properties, biodegradability and surface characteristics, they can be used as a contrast agent for MRI of myocardial infarction and myocarditis experimental models [40]. Furthermore, there are clinical phase III trials using ferumoxytol for detailed characterization of infarct pathology by causing hypoenhancement (in T2-weighted images) and signal void (in T2*-mapping images) [25]. SPIONs also present cardioprotective effects, as Fe_2O_3 NPs coated with dimercaptosuccinic acid decreased ROS production and increased nitric oxide secretion [41]. Another interesting approach was administration of inhalable biodegradable inorganic nanoparticles that can target myocardial cells. Researchers delivered negatively charged calcium phosphate NPs (CaP-NPs), which accumulated into the myocardium 60 min after inhalation. After reaching the intracellular compartment of the myocytes, CaPNPs released a mimetic peptide (R7W-MP) that improved cardiac contractility by targeting the Cavβ2 cytosolic subunit of the L-type calcium channel (LTCC) [42].

Polymeric NPs are one of the largest and most versatile classes of NPs. Their main feature consists of their ability to be designed and tuned in order to accommodate a wide range of molecules (drugs, proteins, nucleic acids) and facilitate a proper release inside the cells. This class of NPs consists of amphiphilic micelles, vesicles, dendrimers and polymerosomes, all of which can be synthetized according to the configuration molecule they are supposed to deliver [43]. These properties are essential in the context of increasing research regarding gene regulation therapies through non-coding RNA and even gene delivery therapies. Out of non-coding RNAs, microRNAs (approx. 23 nucleotides) play important gene-regulatory roles by influencing post-transcriptional repression of coding messenger RNAs [44]. Heart-specific microRNAs have significant roles in cell function, cardiac regeneration and differentiation [10]. Combining polymeric NP composed of poly(9,9-dioctylfluorene-alt-benzothiadiazole) (PBFT) and 1,2-distearoylphosphatidylethanolamine-PEG-amino (DSPEPEG-NH2) is an appealing approach to generate a polymeric matrix for the protection of miR-199a against enzymatic degradation. Experimental studies using an in vivo ischemic heart disease model showed that this miRNA-polymeric nanoparticle combination (miNP) promotes proliferation of endothelial stem-cell-derived cardiomyocytes in the detriment of cardiac fibroblasts, leading to cardiac muscle regeneration and scar reduction [45]. In another study, a pegylated dendrigraft poly-L-lysine (PEG-DGL) dendrimer coupled with an antisense oligonucleotide was used for the inhibition of miR-1. Administration of this miNP succeeded in reducing the extent of the myocardial infarction in mice models, most likely due to the inhibition of miR-1, which has an important role in signaling apoptosis [46]. MicroRNAs also play an important role in regulation of macrophage inflammatory response at the level of the ischemic cardiac tissue. Coupled miR-21, Ca^{2+} and hyaluronan-sulfate NPs (HASCa^{2+}-miRNA) NPs were able to signal a shift of macrophage phenotype from proinflammatory to regenerative state [47].

Dendrimer polymers are also excellent carriers for larger polinucleotidic molecules genes such as small interfering RNAs, messenger RNAs and DNA for the targeted treatment of altered cardiac tissue [48,49]. In an experimental study, a polyethylene-glycol-modified polyamidoamine was loaded with the recombinant plasmid, arginine–glycine–aspartic acid peptide, and hirudine. This novel NP was efficiently used for thrombosis treatment in MI [23]. Finally, polymeric nanoparticles can also be used as promoters and mediators for cell-based therapies. For example, simvastatin-conjugated PLGA NPs can be coupled in vitro with adipose-derived stem cells. This new nanocomplex improved cardiac function as a result of endogenous cardiac-cell regeneration when administered to an MI animal model. The regeneration process was attributed to the constant release of simvastatin from the stem-cell-nanoparticles complex, rather than the direct effect of the stem cells. Furthermore, the number of cells required to deliver this NPs therapy was rather small (10.000 cells/mouse), thus decreasing other risks of cell administration such as thrombosis [50]. Nanoparticles developed for promoting cardiac regeneration are summarized in Table 2.

Table 2. Nanoparticles used for cardiac regeneration.

Nanoparticle Type	Targeted Mechanism	Results
AuNPs coupled with microRNA 155 [38]	• increase expression of anti-inflammatory type 2 macrophages	• reduce myocyte inflammation and apoptosis
Albumin- polyvinyl alcohol-AuNPs nanofibrous scaffolds [39]	• mesenchymal stem cells	• differentiation of stem cells into myocytes and cardiac regeneration after myocardial infarction
Poly(9,9-dioctylfluorene-alt-benzothiadiazole) (PBFT) and 1,2-distearoylphosphatidyl-ethanolamine-PEG-amino encapsulating microRNA-199a [45]	• endothelial stem cells	• differentiation of stem cells into myocytes and cardiac regeneration after myocardial infarction; inhibition of cardiac fibroblasts
Poly-L-lysine (PEG-DGL) dendrimer coupled with an antisense oligonucleotide [46]	• inhibition of microRNA; down regulation of apoptosis	• reduced size of the MI scar tissue
Simvastatin conjugated PLGA loaded in vitro on adipose stem cells [50]	• combined pleiotropic effect of statins with adipose stem cell proliferation	• differentiation of stem cells into myocytes; cardiac regeneration and improved cardiac function

4. Nanomaterial-Based Drug Targeted Therapy for Atherosclerosis

Among CVDs, ischemic heart pathology, which occurs most commonly due to atherosclerotic disease of the heart coronary arteries, is the first cause of death. It is well known that atherosclerosis is a systemic inflammatory disease in which, among accumulation of lipids, a pro-inflammatory state driven by chemokines and leukocytes is the basis in the formation of atherosclerotic plaque [51]. Among traditional risk factors (e.g., LDL-cholesterol) [52], clinical and experimental studies from past years have shown that inflammation plays a causal role in the initiation of the atherosclerosis physiopathology [53]. Usually, the alteration of the endothelial permeability in shear stress arterial segments stimulates the infiltration of the LDL into the intima, which further stimulates the recruitment and adhesion of macrophages to the endothelium. The newly formed foam cells initiate the release of other chemokines, which further trigger supplementary recruitment of inflammatory cells, leading to the development of the fatty streak lesions [54]. Since the lipid and inflammatory cells accumulation is a continuous process, the thinned fibrotic cap is commonly followed by the plaque rupture and thrombus formation. This complication in the evolution of an atherosclerotic plaque is responsible for life-threating clinical scenarios such as myocardial infarction or stroke [55–57].

Although current progress in medicine allows for the development of new modern drugs for the treatment for atherosclerosis, an appropriate level of cholesterol is challenging to achieve even when agents such as statins, fibrates, niacin and antibodies against proprotein convertase subtilisin/kexin type 9 (PCSK9) are used in clinical practice [58]. Thereby, since there is a trend of increasing prevalence of cardiovascular diseases, it is now clear that new pharmaceutical formulations are necessary to improve the prognosis of patients at risk for CVDs.

Recent technological advances made possible the development of several nanoparticles used not only for the diagnosis of cardiovascular diseases, but also for specific drug delivery, usually controlled in the target site by using light, ultrasound and/ or external magnetic field. In the physiopathology of atherosclerosis, the macrophages are the most abundant cells, even in the early stages of the lesion development of the atherosclerotic plaque, and an accumulation of these cells can be observed due to their inability to leave the inflammation site [54], making them a natural target for nanomedicine.

4.1. Nanoparticles Designed for Inhibition of the Foam Cells Development

Currently, nanoparticles are designed and used to interrupt the pathological transformation of macrophages into foam cells due to accumulation of the oxidized LDL cholesterol through the mechanisms mentioned above. Targeting these pathological mechanisms using nanomedicine could be, at least in theory, an efficient approach to prevent the development and progression of the atherosclerotic injury. Lewis et al. showed that by using sugar-based amphiphilic core-shell layered nanoparticles, the uptake of the oxidized lipids into macrophages can be suppressed. Moreover, with the same nanoparticles, they obtained an inhibition of the expression of both MSR1 and CD36 scavenger receptors in macrophages, which shifted from a pro-atherosclerotic into an athero-protective phenotype. When administered in vivo to an animal model of atherosclerotic disease, the treatment with NPs significantly improved the morphology of the lesions. This suggests that NPs protect the endothelial layer against internalization of the oxidized LDL via scavenger receptors and also could block the LDL-induced smooth cell activation and proliferation into the arterial wall [59]. Although suitable for an early stage of atherosclerosis, this approach could be a promising option therapy to inhibit foam cell formation and subsequent pro-inflammatory and pro-atherogenic pathological mechanisms. Another approach for targeting LDL scavenger receptors such as LOX-1, which is expressed in patients with cardiovascular diseases [60], is the development of DNA nanostructures with different geometrical sizes and shapes (e.g., tetrahedral, octahedral nanocages, origami structures). Experimental studies indicate that LOX-1 receptors not only bind but also specifically internalize these DNA nanocages, which paves the way for targeted therapy of the atherosclerotic LOX-1 overexpressing cells [60–62].

Liver X receptors (LXR) are members of the nuclear hormone receptor family of transcription factors and are currently considered as another potential alternative for nanoparticle-based drug-targeted therapy for atherosclerosis. The activation of these receptors in macrophages triggers different atheroprotective effects such as cholesterol efflux, inhibition of inflammation and enhancing the clearance of foam cells by healthy macrophages [63]. Indeed, in an experimental study, Joseph et al. showed that the administration of a nonsteroidal LXR agonist had potent antiatherogenic activity in two distinct animal models of atherosclerosis through direct effects of LXR ligands on macrophages within the artery wall [64]. Unfortunately, the clinical use of LXR agonists is currently unavailable since significant liver steatosis produced by LXR-mediated induction of sterol regulatory element-binding protein-1c gene (SREBP-1c) is a common side effect. To overcome this deleterious effect, Fisher et al. designed and tested the efficacy of poly-lactide-co-glycolide-b-polyethylene glycol (PLGA-b-PEG) containing a synthetic LXR agonist to inhibit the development and progression of atherosclerotic plaque while avoiding liver steatosis. They reported that the PLGA-b-PEG-LXR agonist efficiently suppressed inflammatory factors in macrophages both in vitro and in vivo. Moreover, following systemic administration, PLGA-b-PEG encapsulating LXR agonists were found in significant concentration within plaque macrophages. The authors also reported that animals receiving the PLGA-b-PEG-LXR agonist showed a 50% reduction in the CD 68+ macrophage content in plaques when compared to the PLGA-b-PEG without LXR agonist, suggesting that this innovative formula is able to improve the resolution of inflammation from atherosclerotic plaque while precluding liver steatosis. Given that both PLGA and PEG polymers are already approved for medical applications, the clinical implementation of this approach involving the PLGA-b-PEG-LXR agonist for the treatment of atherosclerosis is likely to be seen in the near feature since the formulation is proven to be biocompatible, biodegradable and safe as a drug carrier while reducing the deleterious effect on liver function [65].

Synthetic high-density lipoprotein (sHDL) nanoparticles have been proven as an encouraging alternative as cholesterol acceptors in patients with atherosclerosis. Hydrophobic core and endogenous atheroma-targeting features of sHDL allow encapsulation of water-insoluble drugs such as LXR agonists. Based on that, Schwendeman et al. tested the efficacy of LXR agonists encapsulated into sHDL nanoparticles on increasing the efflux of

cholesterol from atheroma macrophages. They reported that LXR agonists incapsulated into sHDL nanoparticles were able to induce significant inhibition of atherogenesis in a murine model by enhancing the cholesterol efflux from atheroma macrophages, thus improving efferocytosis and therefore decreasing the inflammation [66].

As mentioned before, in the development of atherosclerosis, microRNAs are involved in the response to shear stress, adhesion-molecule expression, macrophage response to oxidized LDL, neointimal lesion formation, plaque angiogenesis and cellular cholesterol homeostasis. Moreover, several clinical studies focusing on establishing the diagnosis and determining short- and long-term prognosis of patients at risk for CVDs have demonstrated that microRNAs are useful not only in differentiating patients with arterial disease from those with a healthy status, but also in predicting future cardiac events [67]. Among them, microRNA-33 has been considered as a key regulator in atherogenesis, since it is able to modulate cellular lipid metabolism, fatty acid oxidation, macrophage inflammatory polarization and macrophage autophagy [68]. These findings encouraged the strategy to antagonize microRNA-33 and thereby to treat atherosclerotic disease. Since the inflammatory state is a common condition of atherosclerosis and the inflamed tissues are usually characterized by mildly acidic microenvironments, Zhang et al. designed and developed anti-microRNA-33 nanotherapies using cyclo-dextrins derived pH-responsive nanoparticles to antagonize them at the level of inflammatory atherosclerotic lesions. The authors reported that the pH-responsive nanoparticles encapsulating anti-microRNA-33 were able to reduce the amount of altered macrophages from atherosclerotic plaque, diminishing the necrotic area. Thereby, the entire plaque vulnerability was reduced by promoting reverse cholesterol transport and regulating the local immune response via modulation of the macrophage polarization and T cell differentiation [69]. Thus, antagonizing microRNA-33 using nanomedicine seems to be a promising alternative therapy to obtain a proper inhibition of atherosclerotic inflammation, to reduce the plaque vulnerability and thus to improve the prognosis of patients.

4.2. Nanoparticles Designed for the Inhibition of Macrophage Proliferation and/or Accumulation

From a mechanistic point of view, macrophage accumulation followed by their proliferation plays a critical role in the development and inflammatory responses of atherosclerosis. Since macrophage proliferation is the main mechanism that leads to foam cells generation, and given that macrophages are already known to contribute to plaque rupture and thrombosis, interrupting this pathological link could be an appealing approach. In an experimental study using apolipoprotein E-deficient mice with advanced atherosclerotic plaques, Mulder et al. showed that inhibition of macrophage proliferation by using nanoparticle-based delivery of simvastatin have beneficial effects on both plaque inflammation and phenotype remodeling. Moreover, these beneficial effects can be maintained up to 8 weeks when oral statin treatment is administered while eluding any simvastatin harmful effect on liver function. This experimental study demonstrated that aiming the macrophage proliferation into atherosclerotic plaque using nanotherapy is a feasible targeted antiproliferative strategy without adverse effects [70]. In another experimental study, Egashira et al. developed PLGA nanoparticles containing pioglitazone, which is a potent agonist of peroxisome proliferator-activated receptor γ (PPARγ) and is able to impact macrophage polarity by enhancing the expression of anti-inflammatory markers such as CD206 and CD36. In an animal model of atherosclerosis, nanoparticle-mediated delivery of pioglitazone caused inhibition of macrophage activation and also reduced the vulnerability of atherosclerotic plaque by diminishing buried fibrous caps, which is known as a marker of plaque instability [71]. In a recent experimental study, Wang et al. developed biomimetic nanoparticles using macrophage membrane (MM) coating on the surface of rapamycin-loaded poly lactic-co-glycolic acid (PLGA) copolymer to suppress the progression of atherosclerosis by interfering with the macrophage pathway accumulation. After encapsulating PLGA nanoparticles with rapamycin (RAP)—an inhibitor of the mammalian target of RAP pathway—they covered RAP-PLGA nanoparticles with MM to specifically target atherosclerosis sites and release locally anti-atherosclerotic agents to

counteract the progression of the atherosclerotic plaque. The functionalized nanoparticles demonstrated a proper biocompatibility when administered in vivo and also proved to be efficient due to their specific accumulation into lipid lesion. Moreover, by incorporating an anti-atherosclerotic drug inside coated MM RAP-PLGA complex, the authors concluded that these biomimetic nanoparticles notably reduced the progression of atherosclerosis when administered over the long term [72]. Therefore, this novel and provocative approach using cells' membrane-coating nanotechnology could be an encouraging therapy focusing on targeting macrophage accumulation into atherosclerotic lesions.

In another study, Park et al. developed a different type of functionalized nanoparticle designed for atherosclerotic plaque inhibition using cargo-switching nanocomplexes (SCNP). Essentially, they conceived nanoparticles with a core containing a complex of cyclodextrin and simvastatin covered by a shell of phospholipids. Using cyclodextrin to target a cholesterol-rich microenvironment from atherosclerotic plaque, SCNP released a low-affinity hydrophobic drug in the cholesterol-rich atherosclerotic microenvironment and scavenged high-affinity cholesterol within the microenvironment. Additionally, SCNPs demonstrated sustained anti-inflammatory effects in vitro since released statin was able to inhibit the activated macrophages [73]. Therefore, these types of functionalized nanoparticles that are able to exploit various microenvironmental factors from atherosclerotic plaque may be an optimistic approach for targeting different pathological pathways such as locally macrophage-mediated inflammation and/ or interfering with cholesterol-induced atherogenesis. Table 3 summarizes the nanoparticles designed for targeting macrophage pathogenesis.

Table 3. Nanoparticles targeting macrophage pathogenesis.

Nanoparticle Type	Anti-Atherosclerotic Targeted Mechanism	Results
Sugar-based amphiphilic core-shell layered nanoparticles [59]	• inhibition of the uptake of the oxidized lipids into macrophages • inhibition of the expression of MSR1 and CD36 scavenger receptors in macrophages	• protection of the endothelial layer against internalization of the oxidized LDL • inhibition of the LDL-induced smooth cell activation and proliferation into arterial wall
Poly-lactide-co glycolide-b polyethylene glycol (PLGA-b-PEG) containing a synthetic liver X receptor (LXR) agonist [64,65]	• targeted activation of the LXR receptors in macrophages from atherosclerotic plaque	• suppression of the inflammatory macrophages-related factors both in vitro and in vivo studies • significant reduction in the CD 68+ macrophage content in the atherosclerotic plaques
Synthetic high density lipoprotein (sHDL) nanoparticles loaded with LXR [64]	• increase the efflux of cholesterol from atheroma macrophages (efferocytosis)	• improved efferocytosis • inhibition of inflammation from atherosclerotic plaque
Nanoparticles-based delivery of simvastatin [70]	• macrophages proliferation	• inhibition of macrophages proliferation • resolution of plaque inflammation and improved phenotype remodeling
PLGA nanoparticles containing pioglitazone [71]	• macrophage polarity	• inhibition of macrophage activation • reducing the atherosclerotic plaque vulnerability
Biomimetic nanoparticles using macrophage membrane (MM) coating on rapamycin-loaded PLGA polymers [72]	• macrophages accumulation into atherosclerotic plaque targeting rapamycin pathway	• significant reduction of the progression of atherosclerosis

4.3. Nanoparticles Designed for the Inhibition of the Pro-Inflammatory Factors

As mentioned before, atherosclerosis is a systemic inflammatory disease that has a progressive evolution characterized by vascular inflammation, development of atherosclerosis, and plaque rapture, which leads to life-threatening cardiovascular events if the physiopathological mechanisms are not interfered with or interrupted by non-pharmacological or pharmacological targeted therapies [74,75].

Since experimental and clinical studies have demonstrated the implication of pro-atherogenic cytokines such as tumor necrosis alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) in the pathogenesis of atherosclerosis [76], using nanomedicine to target these specific pathways has become an appealing approach. Moreover, current experimental studies are focusing on the modulation of interleukin-10 (IL-10), which is known to have a powerful anti-inflammatory effect and plays a protective role in the pathogenesis of atherosclerosis. This is due to the inhibition of macrophage activation as well as inhibition of matrix metalloproteinase, pro-inflammatory cytokines and cyclooxygenase-2 expression in lipid-loaded and activated macrophage foam cells [77]. Since systemic administration of IL-10 is not feasible due to a short plasma half-life and based on previous results that showed that cyclo-RGD (an avb3 Integrin Binding Cyclic RGD Peptide—cRGD) peptide conjugated pluronic-based nano-carriers (NC) could effectively target the plaques in an animal model of atherosclerosis, Tae et al. proposed the encapsulation of IL-10 together with iron oxide nanoparticles (IONP) into the cRGD peptide conjugated NC to test if this nanocomplex is able to efficiently repress the inflammation from atherosclerotic plaque. The authors showed that encapsulation of the IL-10 into the abovementioned nanocarriers is able to assure a higher level of IL-10 in blood for up to 7 days when compared to free IL-10. They achieved a significant regression up to 30% of the plaque amount, based on the resolution of the inflammation. Furthermore, the authors demonstrated that IL-10 NC complex was efficacious for targeted delivering of the anti-inflammatory cytokine inside the atherosclerotic plaque. Moreover, the authors showed that IL-10 NC significantly suppressed IL-1β into the lipidic lesion, proving that these nanocomplexes are effective for alleviation of the atherosclerotic plaque inflammation [78].

In another recent experimental study, Kim et al. investigated the effects of CD9 antibody-functionalized mesoporous silica nanoparticles (MSN) on the inflammation paralleling atherosclerosis. In vitro experiments reproducing the pathological alteration of senescent macrophages and endothelial cells, the CD9-MSN demonstrated beneficial effects on the atherosclerotic microenvironment enhancing cell viability. Accordingly, they were able to develop a nanocomplex in which rosuvastatin (RSV) was loaded in CD9-modified MSN coated with hyaluronic acid (HA), poly (L-lysine hydrochloride) (PLL), and methoxy-poly (ethylene glycol)-block-poly (L-glutamic acid sodium salt) (PGA): CD9-HMSN@RSV. Results from in vitro and in vivo experiments showed that CD9-HMSN@RSV nanocomplex can target atherosclerotic plaque and also significantly reduced the secretion of TNF-α and IL-6 from the activated macrophages, reduced ROS production and decreased LDL oxidation [79]. Taken together, these encouraging results pave the way to specifically and efficiently target the pro-inflammatory cytokines involved in the pathogenesis of plaque development and to alleviate the evolution of atherosclerosis.

Chemotherapeutic agents such as paclitaxel and docetaxel have intensive anti-proliferative effects since they are able to inhibit the disassemble and promote the polymerization of microtubules [80]. Given that, the incorporation of these anti-cancer drugs into nanoparticles has become an instigative therapeutic strategy since this association is theoretically able to impact the pathogenesis of atherosclerosis [81]. To test the hypothesis that incorporation of docetaxel (DTX) into low density emulsion (LDE) nanoparticles (NPs) has anti-atherosclerotic action, Maranhão et al. accomplished an experimental study in which they administered DTX-LDE NPs to a rabbit model of atherosclerosis. Intriguingly, the DTX-LDE NPs treatment was able to reduce by 80% the atherosclerotic area in the treated group. Additionally, the animals treated with DTX-LDE NPs showed a reduction of pro-inflammatory markers such as TNF-α, IL-1β and IL-6 by approximately 60%. The authors

also showed that administration of DTX-LDE NPs reduced the expression of Nuclear Factor Kappa-light-chain-enhancer of activated B cells (NF-κB) which is known to be involved in the modulation of the cascade of pro-inflammatory cytokines involved in atherosclerosis [82]. These results offer new research perspectives and could represent a real paradigm shift since encapsulated anti-cancer drugs into various type of nanoparticles might be a provocative alternative for the treatment of systemic atherosclerosis.

In another instance, Bartneck et al. demonstrated a different pattern of the action mechanisms of anti-inflammatory glucocorticoid—dexamethasone—when encapsulated into nanocarriers such as liposomes. Interestingly, the authors found that encapsulated dexamethasone into liposomes may have a different mechanism of action than its non-incorporated form since liposomal dexamethasone reduced the expression of TNF-α, IL-1β and IL-6 only under an inflammatory state. Moreover, dexamethasone-loaded liposomes was able to significantly reduce the macrophages and monocyte migration [83]. Although these findings were attained only in in vitro experiments, this approach may be an unconventional strategy for targeted delivery of systemic anti-inflammatory agents such as dexamethasone for the treatment of atherosclerosis. This can potentially have clinical significance, taking into consideration the well-known secondary adverse reactions of the corticoids, which can be partially repressed by this alternative formulation. In Table 4 we summarized the nanoparticles which are targeting pro-inflammatory factors.

Table 4. Nanoparticles targeting pro-inflammatory factors.

Nanoparticle Type	Anti-Atherosclerotic Targeted Mechanism	Results
cRGD peptide conjugated nanocarriers containing IL-10 and iron oxide nanoparticles [78]	• modulation of IL-10	• increased IL-10 concentration into the blood • resolution of inflammation into atherosclerotic plaque • inhibition of IL-1 beta • 30% reduction of plaque size
CD9 antibody-functionalized mesoporous silica nanoparticles [79]	• modulation of the inflammation paralleling atherosclerosis	• reduced the secretion of TNF-alpha and IL-6 • reduced ROS production • decreased LDL oxidation
Low density emulsion nanoparticles containing docetaxel [82]	• inhibition of inflammation	• 60% reduction of pro-inflammatory markers such as TNF-alpha, IL-1beta and IL-6 • reduced the expression of NF-KB of activated B cells
Liposome based nanocarriers containing dexamethasone [83]	• glucocorticoid mediated inflammation	• reduced the expression of TNF-alpha, IL-1beta and IL-6 • reduce the macrophages and monocyte migration

5. Conclusions

Innovation in nanomedicine made possible the development of new multifunctional nanocarriers to specifically deliver therapeutic agents to ischemic and atherosclerotic areas, not only for diagnosis but also for treatment purposes. The progress in nanotechnology in the past years allows for current development of new nanocomposites personalized for drug-targeted therapy of ischemic heart failure and atherosclerosis. This perspective has emerged not only as a key drug targeted therapy for CVDs, but also the capability to become a paradigm shift since nanoparticles open the doors and smooth the path for uncovering new pathological mechanisms.

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