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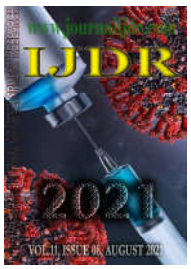

REVIEW ARTICLE OPEN ACCESS

NANOTECHNOLOGY IN VASCULAR MEDICINE A REVIEW

Mirzaie Masoud*[1], Josefina Kusnirova[1], Johann Philipp Addicks[2] and Sheila Fatehpur[1]

[1]Department of Vascular Surgery, OWL, University Clinics, Campus Lemgo, Germany; [2]Institute of Neuroradiology, OWL, Klinikum Lippe University Hospital, Campus Lemgo, Germany

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Corresponding author: Mohammad Nozari

ABSTRACT

Although the application of materials produced in nanotechnology with a size of 1-100 nm in at least one of their dimensions at the molecular level opens new perspectives in the care of patients, the question of cost-effectiveness and the safety of nanotechnology still remain open. These have proven to be useful not only as prosthetic materials, but also for surface preparation of implants and prostheses, effective drug delivery systems for antibiotics, and chemotherapeutics, and drug eluting systems to combat implant-related infections, e.g.. The application of nanotechnology in vascular medicine firstly extends to both drug-eluting therapies for obstructive vascular diseases and prosthetic materials used for surgical revascularization. The novel nanomaterials can deliver the thrombolytic drugs directly to the lesion.

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INTRODUCTION

Although the application of materials produced in nanotechnology with a size of 1-100 nm in at least one of their dimensions at the molecular level opens new perspectives in the care of patients, the question of cost-effectiveness and the safety of nanotechnology still remain open (1). These have proven to be useful not only as prosthetic materials, but also for surface preparation of implants and prostheses, effective drug delivery systems for antibiotics, and chemotherapeutics, and drug eluting systems to combat implant-related infections, etc. (2-4). The application of nanotechnology in vascular medicine firstly extends to both drug-eluting therapies for obstructive vascular diseases and prosthetic materials used for surgical revascularization. The novel nanomaterials can deliver the thrombolytic drugs directly to the lesion (5).

Aim of the review: In the near future, new developments in nanotechnology will make it possible to therapeutically address the underlying mechanisms of atherosclerosis directly at their point of origin and to validly measure the success of therapy using the same method. In doing so, the complications to be feared from systemic therapy can be avoided and the therapeutic dose even reduced. The present work deals with the various facets of the new developments in nanotechnology in the diagnosis and therapy of vascular diseases, especially atherosclerosis.

METHODS

This systematic review was performed using available databases: PubMed, Medline, Cochrane Library, Embase, and Clinical Trials.gov. Unpublished data remained unconsidered. The keywords Key words entered were nanotechnology, vascular disease, molecular biology basis of atherosclerotic plaques, nanostents, nanoprostheses. Only studies that showed a clear result were considered. Pilot studies were not considered.

DISCUSSION

Our current drug therapies are characterized by poor target specificity and too low delivery efficiency (6-8). By altering their shape, size, and surface chemistry, the site-specific delivery of nanoparticles can be specifically programmed (9,10). As a first particle, the use of Doxil, a liposomally encapsulated doxorubicin formulation for the treatment of Kaposi's sarcoma significantly reduced doxorubicin-induced cardiotoxicity and heart failure typical of this treatment by cancer-specific toxicity (11,12). Other nanoparticle drug delivery systems developed on this basis are used in infections, chronic kidney disease, e.g. (13). In vascular medicine, nanoformulations of fenofibrate are used in patients with hypertriglyceridemia. This has completely abolished significant problems associated with the

ingestion of fenofibrates, such as solubility and absorption (14-16). Promising are the new developments with additional nanoparticles for treatment with Annexin A1 mimetic peptide and IL-10 bound to Type IV collagen-targeted copolymers of PLGA-PEG, superoxide dismutase mimetic agent and hydrogen peroxide-eliminating compound, bound to cyclodextrin-based polysaccharide, prednisolone bound to MRI-detectable liposomes, VCAM1, ICAM1 and 2, E- and P-selectin siRNA bound to PEI polymer as some examples (17-29). Appropriate nanoparticles are also being tested for supraselective thrombolytic therapy with streprokinase, urokinase, or thrombin inhibitors (30-35).

The inflammation typical of atherosclerosis is maintained by a lack of programmed cellular clearance of apoptotic cells (36-38). Their suppression by canakinumab carries the risk of decreased innate immunity and increased mortality (39-41). Nanoparticles acting only on atherosclerotic plaques may minimize this risk (41). The principle of action of this procedure can be attributed to the specific function of type IV collagen, the release of which plays a central role in vascular injury and inflammation (42). Binding of annexin A1-derived peptide to a type IV collagen targeting peptide resulted in a 70% increase in nanoparticle selectivity for atherosclerotic lesions (43). A similar effect was achieved by binding anti-inflammatory cytokine IL (interleukin)-10 to type IV collagen-targeted copolymers of PLGA-PEG (18). In addition, nanoparticles can be used theranostically (therapeutic-diagnostic). In animal studies, binding of prednisolosn to an MRI-detectable liposome prolonged its half-life, without systemic toxicity, and demonstrated a sustained decrease in plaque inflammation on 18F-FDG positron emission tomography/computed tomography (44-46).

In another animal study, binding of small interfering RNA (siRNA) directed against multiple adhesion molecules to a polymer-based nanoparticle significantly reduced tissue damage and necrotic core formation after coronary ligation following an ischemic insult (47,48). Neointimal neovascularization significantly correlates with increased plaque instability and subsequent symptoms (49-51). This process is triggered by VEGF (vascular endothelial growth factor) and platelet-derived growth factor, among others. Anti-VEGF therapy, mainly by binding VCAM1, ICAM1 and 2, E- and P-selectin siRNA to a PEI polymer, reduced plaque development in apoE-/- mice. At the same time, the MRI-detectable nanoparticles allowed the T1-weighted MRI signal to be measured in the aorta as a parameter of inflammation and thus could be evaluated diagnostically (47,52-57). A central role in the pathogenesis of atherosclerosis beyond lesion initiation is played by macrophages, especially in misdirection of apoptotic cells in terms of efferocytic activity (58,59). Several nanotherapies target monocyte recruitment and infiltration in plaque, proliferation of macrophages with polarization to a less inflammatory M2 phenotype, and cholesterol metabolism (14-16,22,25,60). Nanoparticles were also shown to inhibit the uptake of oxidized LDL by macrophage SRs (scavenger receptors), resulting in a reduction of lipid load and thereby decreased reduced plaque occlusion in the aorta of ApoE-/-mice (24).

Binding of TRAF6 inhibitors into recombinant high-density lipoprotein (HDL) nanoparticles (TRAF6i-HDL) blocked cluster of differentiation 40 (CD40)-induced TRAF6 (tumor necrosis receptor-associated factor 6) in monocytes and macrophages, resulting in stable plaque phenotypes and no adverse immune responses (18,26,61). The combination of nanotherapy with phototherapy gave rise to controversial discussions. Phototherapy with near-infrared fluorophore of inflammatory monocytes and macrophages that have previously ingested iron oxide nanoparticles not infrequently results in ablation of macrophage-rich plaques in animal studies (62,63). This may increase the risk of plaque rupture (64). Precisely to avoid this highly dangerous side effect, cell-specific single-walled carbon nanotubes (SWNTs) that are highly selectively taken up by inflammatory Ly-6Chi monocytes are increasingly being developed (65). In this context, their natural photoacoustic contrast and a near-infrared fluorescence signal open additional diagnostic possibilities of SWNTs (66). Anti-stenotic agents used for targeted inhibition of restenosis after peripheral revascularization can act directly on the treated vascular bed by binding to nanoparticles (67,68). For example, supraselective endovascular delivery of albumin-bound rapamycin nanoparticles reduced luminal stenosis after balloon angioplasty of the femoral artery in a porcine model (69). Similar results were obtained in another study using αvβ3-targeted paramagnetic nanoparticles for the delivery of rapamycin (70-72). In the new generations of drug-eluting stents, paclitaxel bound to nanoparticles is attached to surfaces of stents (73). This has already yielded promising results in animal studies (74-76). Thus, even much higher doses of paclitaxel could be tolerated (77-80). Similar results were obtained in animal studies as well as in clinical trials with liposomal formulation of the bisphosphonate alendronate. Although a significant difference in restenosis rate was found between the treatment and placebo groups, the rate of in-stent late loss was significantly lower in patients with an elevated monocyte count at baseline (81). One of the major challenges in interventional therapy is instenosis. The restenosis rate of 40% in the treatment of coronary artery disease with a drug-eluting stent and in the treatment of femoral artery stenosis after only 24 months was not different from that of the pacebo group of 44% (82). In addition, the paclitaxel- and sirolimus-eluting stents exhibit significantly higher rates of thrombosis via slowed endothelialization, which can be lethal, especially with poly-n-butyl methacrylate- and polyethylene-vinyl acetate copolymer-eluting prostheses (83-85). Microfabricated drug-release reservoirs used in two new stents (the Janus CarboStent, Sorin Biomedica Cardio S.p.A., Via Crescentino, Italy, and the Conor Stent, Conor Medsystems, Inc, Menlo Park, California) are promising (86).

In this context, neointima hyperplasia is affected more by a prolonged release phase than by the dose itself (87,88). Future directions include stents fabricated by microelectroerosion machining (μEDM) (89,90). A different manufacturing technique using sharp silicon microneedles with a height of 80 to 140 μm allow local accumulation of therapeutic agents by penetrating dense atherosclerotic lesions (91). Technical difficulties hamper the implementation of this development (92,93). As a new generation of medicinal agents as nanoscale texture hydroxyapatite and titanium oxide in development (94-98). Electrospun poly ε-caprolactone nanofiber scaffold (PCL), which is hydrophobic due to surface modification with gelatin and architecturally mimics ECM, represent new generation of vascular prostheses (99-105). The poor long-term results caused by lack of geometric alignment of previously used prostheses such as PTFE and Dacron could be compensated by the development of electrospun scaffolds (ES) (106-110). Endothelial injury induced during angioplasty represents one of the main initiators of intimal hyperplasia, which could be reduced in a dose-dependent manner by doxorubicin-loaded nanoparticles in a rat model (111,112). Polyhedral oligomeric silsesquioxane (POSS) and polyhedral oligomeric silsesquioxane poly (carbonate-urea)-urethane (POSS-PCU) used to coat new generation prostheses are characterized by their antithrombogenic properties as well as stimulation of endothelialization (113-115). Also in valve replacement surgery, polymeric heart valves (PHVs) represent an alternative to existing prostheses whose use in routine clinical practice will certainly take years (116-119). Based on a functionalized graphene oxide (FGO) nanomaterials in a poly(carbonate urea) urethane (PCU) backbone, the nanotechnology-based prosthesis, Hastalex has shown good results in vivo trials (120).

Conclusions

The multiple developments in nanotechnology not only enable a new therapeutic approach to specifically modify atherosclerotic plaque at the molecular level, but at the same time allow verification of therapeutic efficacy. As a result, non-lower single therapeutic doses of drugs can be administered. The side effects occurring in the process can also be reduced to a minimum. The new generation of bioprostheses based on nanotechnology will revolutionize the long-term results of vascular interventions.

List of abbreviations

VCAM1: Vascular Cell Adhesion Protein 1
ICAM1: Intercellular Adhesion Molecule
PEI polymer: Polyethylenimin polymer
PLGA-PEG: poly-Lactide-Co-Glycolide A-PpolyEthylene Glycol
VEGF: Vascular Endothelial Growth Factor
MRI: Magnet Resonance Imaging
TRAF6: tumor necrosis receptor-associated factor 6
SWNTs: single-walled carbon nanotubes
µEDM: microelectroerosion machining
PCL: poly ε-caprolactone nanofiber scaffold
ECM: extracellular matrix
PTFE: Polytetrafluorethylen
ES: electrospun scaffolds
POSS: Polyhedral oligomeric silsesquioxane
POSS-PCU: polyhedral oligomeric silsesquioxane poly(carbonate-urea)-urethane
PHVs: polymeric heart valves
FGO: functionalized graphene oxide

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