Expert Opinion

The promise of nanotechnology for heart, lung and blood diseases

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Nanotechnology offers a broad range of opportunities for improving the diagnosis and therapy for heart, lung and blood diseases, and drug delivery represents an area of particular promise. For cardiovascular disease, the treatment of atherosclerotic plaque and prevention of restenosis following stent placement offer attractive targets for nanotechnology. In lung disease, nanotechnology may provide novel treatments for a broad range of intractable pulmonary diseases, including bacterial biofilms, fungal infections, and tuberculosis. For haematopoietic diseases, targeted delivery of drugs to lymphocytes may represent a strategy for reducing systemic cytotoxicity. This editorial discusses some of the more promising targets for nanotechnology-based treatment of heart, lung and blood diseases.

Keywords: cardiovascular, haemopoietic, nanotechnology, pulmonary, targeted delivery

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1. Introduction

The use of nanoparticles for drug delivery offers a number of potential advantages. At the most basic level, encapsulation of drugs in nanoparticles can help to solubilise poorly soluble drugs and enhance pharmacokinetics by extended release of the drug. Targeting of nanoparticles to specific sites in the body, by targeting specific cell surface receptors, for example, can improve delivery of drug to the intended target while reducing the systemic load. Nanoparticles can be designed to release their load in response to the local environment, such as in response to pH changes, for example.

2. Organ-specific examples of nanotechnology application

2.1 Cardiovascular disease

The development of atherosclerotic plaque plays a primary role in both myocardial infarction and stroke, two of the leading causes of death in the US. The development of plaque leads to expansion of the vasa vasorum, which are the network of small blood vessels in the walls of large blood vessels. Blockade of plaque neovascularisation has been proposed as a therapeutic strategy to reduce inflammation and progression of advanced atherosclerosis. Immature neovessels express cell-surface markers that are not found on mature vessels, including the $\alpha_v\beta_3$ integrin. Perfluorocarbon nanoparticles targeted to the $\alpha_v\beta_3$ integrin through a surface-bound antibody have been used to both deliver an antiangiogenic drug, fumagillin, to the newly formed vasa vasorum, and to image the progress of therapy through gadolinium and MRI. The binding of the nanoparticles to cells through cell-surface receptors has been shown to allow rapid transport of the drug from the outer drug-loaded lipid monolayer to the cell membrane, through a process termed contact-facilitated drug delivery [1].

Nanoporous coatings are being tested for drug-eluting stents, seeking to take advantage of the potential for programmable pharmacokinetic capacity using advances in nanotechnology. These coatings may allow more precise and controlled release of less toxic and improved molecules. Systemic administration of nanoparticles

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has also been used to prevent neointimal proliferation in animal models of vascular injury; the administration of doxorubicin in core-shell nanoparticles of PEG-based block copolymer achieved a higher tissue concentration of the drug at the injury site, compared with systemic delivery of the free drug, and resulted in decreased neointimal formation. In this case, the uptake of nanoparticles occurs via passive targeting to the tissue, which displays sustained hyperpermeability following balloon damage [2]. Active targeting of nanoparticles to markers expressed following tissue damage would potentially increase local drug delivery. Local delivery of drug-containing nanoparticles using a drug delivery balloon catheter may also provide an effective therapeutic option for the prevention of restenosis [3]. Effective systemic or local nanoparticle-mediated drug delivery could mitigate restenosis problems resulting from the use of bare-metal stents, making them a more viable and possibly cheaper alternative to expensive drug-eluting stents.

2.2 Pulmonary disease

The potential for nanotechnology to impact the delivery of therapy to the lungs is high, reflecting the additional opportunities that inhalational delivery offers. Inhaled drug delivery in the form of dry powder or suspension aerosol suffers from a number of potential disadvantages. Poor solubility and a microparticulate nature can limit diffusion and dissolution of the drug at the site of action, and therefore limiting bioavailability. The residence time of drugs can be limited by rapid ciliary clearance and alveolar macrophage uptake, thus abolishing long-term effects. In contrast, the use of nanoparticles and nanosuspensions offers a number of potential advantages:

- rapid onset of action resulting from fast diffusion and dissolution of the drug;
- increased adhesion of nanoparticulate drug to mucosal surfaces can provide extended residence time of the drug at the site of action;
- phagocytic clearance of nanoparticles is lower relative to larger particles in the µm range.

The optimal particle size for delivery to the deep lung is 1 – 5 µm. Penetration of nanoparticles into the deep lung will be limited by their low inertia, resulting in low-lung deposition and exhalation. However, a number of methods have been developed to deliver different types of nanoparticulate drug formulations to the deep lung. These include aerosol delivery of nanosuspensions of the drug, a method useful for drugs that are water insoluble but soluble in oil; and microencapsulation of chitosan nanoparticles for lung-protein delivery.

The potential for inhaled nanoparticles is now being tested for a number of pulmonary diseases. Oral antitubercular therapy for pulmonary tuberculosis requires high-drug doses in order to achieve therapeutic doses to the lung, and rapid clearance results in a need for daily treatment with multiple drugs for extended periods of time. Nanoparticle delivery of antitubercular drugs shows great promise, resulting in the sustained maintenance of therapeutic concentrations both in the lungs and systemically [4]. The delivery of antitubercular drugs via inhaled nanoparticles at 10-day intervals provided effective treatment in animal models [5]. Less frequent dosing would be valuable clinically, potentially improving patient compliance and decreasing cost.

Nanoparticles show promise for the delivery of small interfering RNA (siRNA) and gene therapy. Prophylactic intranasal treatment of mice with siRNA to a respiratory syncytial virus protein resulted in a dramatic decrease in lung viral titre, as well as decreased inflammation and airway reactivity following infection [6]. DNA nanoparticles are also being developed for the treatment of cystic fibrosis. Mutations in the cystic fibrosis transmembrane regulator (*CFTR*) gene cause aberrant ion transport across epithelial cell membranes. In the lung, this results in thick mucus secretions, which in turn cause recurrent lung infections. Intranasal administration of DNA nanoparticles encoding wild-type CFTR was tested in a Phase I clinical trial for the treatment of cystic fibrosis, and was demonstrated to be safe, and to result in partial to complete nasal CFTR chloride channel reconstitution [7]. Aerosol preparations of the compacted DNA retain full biological activity, and, therefore, lung dosing should be feasible.

Other pulmonary targets for which nanoparticles may have a therapeutic role include fungal infections and bacterial biofilms. Nanoencapsulation of toxic drugs is showing great potential for the treatment of refractory pulmonary mycoses and other lung infections. The treatment of mycoses with amphotericin B is complicated by adverse effects, including nephrotoxicity. Systemic administration of NS-718 (amphotericin B-containing nanoparticles composed of soybean oil and egg lecithin), seems to be promising as a treatment for pulmonary aspergillosis [8].

2.3 Haematopoietic disease

Targeted delivery of drugs to specific haematopoietic cell types is likely to be the main application of nanotechnology to blood diseases. Targeting of gelatin nanoparticles to leukaemic cells and primary T lymphocytes was achieved using anti-CD3 antibodies, and resulted in the internalisation of the nanoparticles into the cells [9]. This strategy has the potential to allow targeting of cytotoxic drugs to the tumour cells, allowing lower drug doses to be used, and reducing systemic toxicity.

Nanoparticles may also represent a novel route for delivering antigens to dendritic cells for vaccine development. Polystyrene nanospheres were efficiently taken up by bone marrow-derived dendritic cells, and activated antigen-specific IFN-γ-producing T cells strongly [10]. These results and other studies suggest that nanoparticles are efficient delivery systems for targeting vaccine antigens to dendritic cells, and for the activation of potent T-cell responses.

3. Expert opinion

Nanotechnology provides an enormous potential for improving drug delivery through a variety of mechanisms. A wide

range of nanoparticle structures, including solid particles, nanoshells, polymeric micelles, liposomes and dendrimers, provide a flexible range of opportunities that can be tailored to meet different therapeutic needs. Targeted delivery of drugs can be achieved by passive targeting to regions of vascular hyperpermeability caused by injury, for example, or by active targeting to cell surface ligands such as receptors and integrins. Active targeting is performed by incorporating targeting moieties, such as monoclonal antibodies or fragments, peptides or peptidomimetics, onto the nanoparticle surface. Cell permeation peptides such as the transactivating transcriptional activator (TAT) peptide can also be placed on the nanoparticle surface to promote particle internalisation. By extension, targeting to specific organelles such as the mitochondria is also feasible using appropriate localisation signals. The targeting of drugs can increase the effective dose of the drug at the target site, reducing the amount of drug that needs to be given and decreasing toxic side effects. In the lung, inhalational delivery of drug formulated in nanoparticles or nanosuspensions can similarly increase the effective dose of drug delivered to the target cells. Controlling nanoparticle composition gives the potential for a more rapid or more sustained release. Environment-sensing nanoparticles can be designed to modify drug release in response to pH, giving the potential for local delivery in response to an acidic environment (e.g., in tumours or ischaemic tissue). The application of these technologies to heart, lung and blood diseases is likely to increase rapidly in the coming years.

Bibliography

1. CYRUS T, WINTER PM, CARUTHERS SD, WICKLINE SA, LANZA GM: Magnetic resonance nanoparticles for cardiovascular molecular imaging and therapy. *Expert Rev. Cardiovasc. Ther.* (2005) 3:705-715.
2. UWATOKU T, SHIMOKAWA H, ABE K *et al.*: Application of nanoparticles technology for the prevention of restenosis after balloon injury in rats. *Circ. Res.* (2003) 92:e62-e69.
3. NANAI S, CHORNY M, GERTZ AD *et al.*: Locally delivered nanoencapsulated tyrphostin (AGL-2043) reduces neointima formation in balloon-injured rat carotid and stented porcine coronary arteries. *Biomaterials* (2005) 26:451-461.
4. PANDEY R, KHULLER GK: Antitubercular inhaled therapy: opportunities, progress and challenges. *J. Antimicrob. Chemother.* (2005) 55:430-435.
5. PANDEY R, SHARMA A, ZAHOOR A, SHARMA S, KHULLER GK, PRASAD B: Poly (D,L-lactide-co-glycolide) nanoparticles-based inhalable sustained drug delivery system for experimental tuberculosis. *J. Antimicrob. Chemother.* (2003) 52:981-986.
6. ZHANG W, YANG H, MOHAPATRA S *et al.*: Inhibition of respiratory synctial virus infection with intranasal siRNA nanoparticles targeting the viral NS1 gene. *Nat. Med.* (2005) 11:56-62.
7. KONSTAN MW, DAVIS PB, WAGENER JS *et al.*: Compacted DNA nanoparticles administered to the nasal mucosa of cystric fibrosis subjects are safe and demonstrate partial to complete cystic fibrosis transmembrane regulator reconstitution. *Hum. Gene Ther.* (2005) 15:1255-1269.
8. OTSUBO T, MAESAKI S, HOSSAIN MS *et al.*: *In vitro* and *in vivo* activities of NS-718, a new lipid nanosphere incorporating amphotericin B, against *Aspergillus fumigatus*. *Antimicrob. Agents Chemother.* (1999) 43:471-475.
9. DINAUER N, BALTHASAR S, WEBER C, KREUTER J, LANGER K, VON BRIESEN H: Selective targeting of antibody-conjugated nanoparticles to leukemic cells and primary T-lymphocytes. *Biomaterials* (2005) 26:5898-5906.
10. WANG X, UTO T, SATO K *et al.*: Potent activation of antigen-specific T cells by antigen-loaded nanospheres. *Immunol. Lett.* (2005) 98:123-130.

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