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The Second Annual Symposium on Nanomedicine and Drug Delivery: exploring recent developments and assessing major advances. 19-20 August, 2004, Polytechnic University, Brooklyn, NY, USA

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Abstract

The meeting was dedicated to novel aspects of nanomedicine including polymer drug delivery systems (DDS) and biomaterials. Self-assembled micellar DDS have been evaluated in term of morphology, biological properties, and results of clinical trials. Important advances in design of nanoparticles as DDS have been highlighted in various presentations. Unexpected issues of polymer-related biological effects, including gene expression, were stressed in relation to polymer DDS. Great potential of nanofabrication of biomaterials, and preliminary data on design of polymer scaffolds were demonstrated in a number of reports. This symposium demonstrated how timely is the development of nanosized DDS with advances in understanding the disease-related mechanisms, and outlined major area of application of nanomedicine technology.

Keywords

biomaterials; nanofibers; nanogels; nanomedicine; polymer micelles; polymer scaffolds

1. Meeting summary

Historically, nanomedicine approaches have been first applied to drug delivery. The most advanced and close to clinical practice drug delivery systems (DDS) are liposomes, hydrophobic drug-encapsulating lipid containers of submicron size range. Many liposomal drug forms have entered clinical trials. However, there are many properties of liposomes, which are poorly compatible with therapeutic applications, for example, preparation, suspension instability, and dry storage incapability. Therefore, an active search for the alternative drug carriers is continued. One of them, polymer-based DDS, progress in the development and their nanomedicine applications have been major issue on the program of the Second Annual Symposium on Nanomedicine and Drug Delivery held in Brooklyn, New York. An important part of the meeting was focused on self-assembled micellar DDS and examples of their successful application as novel drug forms and in developmental therapies. K Kataoka (Tokyo University) has greatly contributed to the design of smart polymeric micelles as DDS for cancer chemotherapy, photodynamic therapy and gene therapy. Kataoka has developed an innovative micellar formulation of cisplatin (CDDP) based on PEG-polyaspartate block copolymers (Figure) that displayed sustained drug release and protection compared to injected cisplatin. Since tumor vasculature is leaky, accumulation of the loaded micelles via enhanced permeability and retention (EPR) effect significantly enhanced efficacy of the therapy (4–5

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injections bi-daily) expressed in the reduction of animal death to 10% in 30 days in comparison with 100% mortality in 8 days for cisplatin alone. Second generation of micellar DDS has included stimulus-activated carriers, which are capable of enhancing an intracellular drug release. Conjugation of adrianomycin to polymer through pH-sensitive hydrazone linkage was an efficient way to trigger drug release following accumulation of drug-encapsulating micelles in endosomes with average pH 5. Another approach to drug activation called photodynamic therapy is based on novel photosensitizers, ionic dendritic porphyrins. Drug-loaded photosensitized micelles are able to release drugs after irradiation markedly increasing drug cytotoxicity in cancer cells compared to free drug or polymer drug formulation without irradiation [1,2].

An understanding of structures forming at the self-assembly of polymer molecules and processes favoring specific architecture of particles is of major interest at the development of polymer DDS. A Eisenberg (McGill University) has pioneered in this area and here presented results of his studies on multiple morphologies of polymer micelles. Eisenberg described approaches to control micellar size, water content and polymer segregation by ensuring slow energetically preferred process of polymer chain distribution. Application of charged block copolymers of PEG-polyacrylate with different block length at low pH may result in formation of hollow vesicles, which are capable to encapsulate drug molecules in internal volume. Otherwise, triblock copolymers of polyacrylic acid, polystyrene and polyvinylpyridine formed differently charged micelles at different pH, with positive surface charge in the presence of hydrochloric acid, or with negative charge in the presence of sodium hydroxide. These data could be helpful, however at the present mostly in a theoretical aspect, in creating various polymer DDS [3,4].

G Kwon (University of Wisconsin, School of Pharmacy) has presented recent advances in development of polymer micelles and supramolecular core-shell structures. The drug could be bound in those structures to the core-forming part of polymer via degradable bonds. PEG-poly-L-lactate readily assembled into micelles that efficiently solubilized an anticancer agent, paclitaxel. This system was significantly less toxic compared to the commercial solubilizing agent, Cremophor® EL (BASF Corporation), used in paclitaxel formulations. The micellar DDS has provided a potent anticancer effect, which was comparable to free drug in animal models, but showed fewer toxic by-effects *in vivo*. Among other examples, Amphotericin B, a drug against hospital-related fungal disease of blood, can be efficiently encapsulated into PEG-poly(acyl)aspartate micelles, which resulted in a lower systemic toxicity. An antifungal activity of the encapsulated drug was the same as that of Fungizone®, but the formulation was significantly less toxic to erythrocytes at doses as low as 0.5 mg/kg [5,6]. Evidently, these biocompatible micellar DDS have a great promise for fast clinical evaluation.

An interesting approach to drug encapsulation, described by K Ulrich (Rutgers State University of New Jersey), was developed in the area of biodegradable and biocompatible amphiphilic star-like macromolecules (ASM) with a well-defined core structure. The ASM are built from polyol center block connected to PEG molecules and have size of ≤ 20 nm. Two zones are formed, drug-binding core with capacity up to 30% by weight and PEG protective shield, which can also be modified by folate for tumor targeting. Small size of the DDS may greatly enhance penetration of drugs into tumor vasculature. Another type of carrier, called amphiphilic scorpion-like micelles with cross-linked core were found to carry more drugs than non-linked micelles of the same size. Well-defined structure and low cellular toxicity of these carriers are beyond questioning advantages of the type of DDS [7].

Several novel types of other DDS with well-defined structure have been highlighted in the presentations of other participants and the following discussions. D Discher (University of Pennsylvania) has described preparation of worm-like micellar carriers and synthetic phages

from PEG-phospholipid vesicles by extrusion through nanoporous filter. These structures following the i.v. administration have shown an extended circulation in the blood and accumulated in tumor site because of enhanced permeability and retention (EPR) effect reaching maximum at 48 h post-injection. Significant three-fold increase of the accumulation was achieved also by attachment of human transferrin receptor-specific peptides. Those targeting peptides were selected by phage panning and have a binding site different of transferrin binding site [8]. The active targeting is certainly a method of choice to avoid non-specific drug biodistribution and shift drug accumulation pattern in desired direction compared to passive (EPR) targeting.

Novel approaches to fabrication of polymer scaffolds and their applications nanomedicine have been analyzed in a presentation by K Leong (John Hopkins School of Medicine). Leong described another type of biocompatible nanomaterial, polyphosphoester nanofibers with diameter 0.2–1.3 micron obtained by electrospining. Galactose-derivatized fibers provided excellent matrix for programmed alignment of endothelial cells and could be used for tissue engineering. Original approach to fabrication of nanofibers by interfacial complexation of polyelectrolytes with opposite charges was developed on the bases of water-soluble chitin as positively charged biocompatible polymer and alginate or hyaluronic acid as negatively charged ones. During this mild process many biological agents (drugs, proteins) could be encapsulated in these biocompatible nanofibers. Release of low-molecular weight drugs is fast (100% in 2 h), due to the lateral diffusion of the drug, whereas proteins showed sustained release up to 35 days well explained by biodegradation of nanofibers matrix. Nanofibers formulated with growth factors and adhesion molecules may be combined for fabricating multilayers and networks with living cells [9,10]. Elegancy of this approach makes it very attractive for development of artificial tissues as a first step to organ design.

The presentation of A Kabanov (University of Nebraska Medical Center) has illustrated an importance of polymer genomics. Studying side effects of many polymers generally regarded as safe substances is becoming a central issue in the development of polymer DDS. Using example of Pluronic® (BASF Corporation) block copolymers for treatment of drug-resistant cancer and for gene therapy applications, he has demonstrated that treatment by the polymers affected not only the function of various cellular structures like membrane-related efflux transporters and mitochondria, but it has a potent modulating effect on the expression of many genes themselves. Concerning new promising polymer DDS, Kabanov has also referred to nanogel carriers developed with S Vinogradov (University of Nebraska Medical Center) and mentioned their application for oligonucleotides delivery to the central nervous system, for systemic treatment of cancer by nucleoside analogues, and for protein formulation. Nanogel carriers consist of cross-linked network of neutral and chargeable (poly[acrylic] acid or polyethylenimine) polymers, include ≤ 95% of water, and well-adopted for systemic administration. Kabanov mentioned a great potential of this type of nanosized DDS for development of ‘smart’ carriers with triggered drug release [11,12]. Unique properties of the nanogel carriers, such as a simple drug encapsulation procedure and convenient lyophilized storage form, make them promising candidates for delivery high-molecular therapeutics including DNA vaccines, plasmid DNA and bioactive proteins.

A similar DDS system was described in a presentation of J DeSimone (North Caroline State University). DeSimone reported synthesis of nanogel drug delivery systems made of PEG-polyacrylate network with quaternized ammonium pendant groups. He highlighted major problem encountered on the way to application of the DDS, which is related to efficiency of intracellular drug release. In order to ensure, for example, an efficient release of antisense oligos from nanogel, the carrier should be engineered the way to quickly disrupt endosomes and then undergo degradation in cytosol. Another discussed aspect of the PEG-acrylate network application was nanofabrication of gel structures with controllable shapes. The author

used a method of non-wetting imprint lithography on polytetrafluoroethylene templates to print PEG-polyacrylate nanoparticles of any predesigned form and size (~ 0.2 μm). These nanogel particles were able to form secondary structures like rolls, as well as they could be post-synthetically modified by targeting or active moieties [13]. Though it is not clear how this fabrication approach can be applied to production of the sufficient amount of drug-loaded nanogel particles, and the author has proposed them as an example of his developed methodology, which undoubtedly allows us to make a big step ahead in nanotechnology.

Another method of nanogel preparation was presented by K Levon (Poly University in Brooklyn), which has focused on preparation of multifunctional lipobeads and nanogels as carriers for small interfering RNA. This new class of drug carriers represents hybrid liposomes with supportive gel inside. Liposome reactor was used to polymerize polyacrylate gels inside liposomes to produce particles with narrow size distribution, and then phospholipids could be removed away by detergent. This technique can also be applied also in the area of micro-assembling and constructing stimuli-reactive carriers [14]. This interesting approach uses existing apparatus to produce biocompatible drug-loaded DDS and well-adopted for fabrication of targeted nanocarriers.

Development of some of nanogel systems has made significant step in the direction of clinical trials. For example, E Turos (University of South Florida) described an interesting approach to preparation of polymer-drug conjugates and formulation of nanoparticles on their base. Microemulsion polymerization of ethyl acrylate monomers and 1–15% of antibiotic drug-binding acrylate monomer was used to produce drug-loaded nanoparticles with size 40–70 nm. Significantly more effective antimicrobial formulations of N-thiolated lactame and Cypro antibiotics have been obtained in form of polymer nanoparticles [15]. Biodegradable bond allows for sustained release of antibiotics *in vivo*, and their application to Phase I clinical trials make these formulations one of the most advanced drug-encapsulating polymer DDS.

2. Expert opinion and conclusion

Summarizing topics presented at this year's symposium, it becomes clear that DDS are indispensable for application of poorly water-soluble drugs, easy biodegradable molecules, or compounds with high systemic toxicity. Drug transport across many biological barriers is sometimes hampered by cellular protective systems against exobiotics. Direct drug targeting by conjugating of the drug molecule with vector moieties may be expensive and reduce drug activity. Therefore, submicron carriers loading extensive amount of drug represent a better choice. Current DDS are based primarily on passive mechanisms of drug release, such as carrier biodegradation or dissociation of micelles. They are the most advanced and well-understood DDS, and several candidates for clinical trials have already been identified among these systems. However, first examples of the second generation of DDS have now appeared, including external stimuli-reactive carriers, which are capable of releasing drugs following irradiation, changes in pH or temperature. Biopolymer application to nanomedicine will also include self-assembling submicron structures or scaffolds with sustained release of drugs or biological factors necessary for cellular/tissue engineering. Significance of these approaches to nanofabrication of biocompatible materials cannot be omitted from overall analysis of current state-of-art in the nanomedicine area.

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