Editorial

Applications of Peptides in Nanotechnology

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Besides their use in the direct therapy of human diseases, peptides can also be applied widely in various fields such as nanotechnology and drug delivery [1, 2]. Peptides have been applied directly as drug delivery vehicles. Such peptides as cell-penetrating peptide (CPP), somatostatin and bombesin have been coupled with drugs, forming peptide-drug conjugates. These conjucates then can deliver the drugs to target sites, either by the CPPs penetrating the cell membrane or the peptides interacting with their cognate membrane receptors [2, 3]. Also, peptides have been combined with nanotechnology for drug delivery [4]. Innovative strategies in applying nanotechnology in drug formulations have been introduced for drug delivery for decades [5]. Nanotechnology such as liposomes, solid-lipid nanoparticles and micelles can deliver various components, such as small molecule drugs, nucleic acids and other peptides via targeted, oral, nasal and epidermal drug delivery. Peptides in combination with nanotechnology are more effective, specific and selective in drug delivery. These combination approaches can directly deliver drugs to targeted cells and reduce toxic side effects [6].

In this thematic issue, we focus on the applications of peptides in combination with nanotechnology for drug delivery. Review articles have been collected globally. Dr. Torchilin reviews the applications of nanotechnology in improving peptide therapeutics. Dr. Chithrani reviews gold nanoparticles for improved therapeutics, with Dr. Yu on self-assembling peptide-based nanomaterials. Dr. Florindo discusses the advances in the applications of peptides in combination with nanoscale systems for cancer vaccines. Advances in peptide modules for use with nucleic acids are reviewed by Dr. Kiselev, while integrin-targeted peptide-drug conjugates are discussed by Dr. Belvisi. We believe these articles will help scientists to become familiar with the current advances in the applications of peptides and nanotechnology combined. Also in this issue, Dr. Gentilucci and Dr. Fregona address peptidomimetics and their applications, respectively.

Dr. Torchilin gives a systematic review of the applications of peptides in nanotechnology. Peptides can be covalently conjugated or physically encapsulated into nanomaterials (micelles, liposomes, solid-lipid nanoparticles) to improve their *in vivo* efficacy. Nanocarriers are used for therapeutic peptide drug delivery [4], such as surfactant-based nanocarriers (microemulsion), lipid-based nanocarriers (solid-lipid and liposomes), polymer-based nanocarriers (hydrogels and micelles) and inorganic nanocarriers (carbon nanotubes, quantum dots and gold nanoparticles). He also addresses how to chemically attach peptides to nanocarriers. Nanosized formulations are a form of passive delivery and have limited drug deposition and retention. Targeting agents, such as peptides, have higher specificity and smaller size. Peptides such as CPPs and phage peptide-based targeting, serve as potential drug delivery vehicles to internalize drugs into cells [7]. Vasculature-targeting peptides such as RGD and NGR (asparagines-glycine-arginine) target tumor vasculature. Anti-angiogenesis and anti-cancer agents can co-encapsulate into RGD-modified liposomes. This is more effective in anti-cancer combination therapy. This review focuses on how nanotechnology can improve peptide applications and discusses the strategies for encapsulation and conjugation of the peptides into nanocarriers.

In his review, Dr. Chithrani addresses gold nanoparticles (GNPs), one type of nanoparticle system, that have been developed as therapeutic and diagnostic agents [8]. GNPs can be different sizes, from 2 to 100 nm, with different shapes, such as spheres and rods. GNPs can also be internalized by receptor-mediated endocytosis, but may be trapped in the endosome and not get into the nucleus. The use of peptides to cover the surface of GNPs may increase nuclear targeting of GNPs by targeting the nucleus. Nuclear-targeting GNPs could effectively deliver drugs into target sites, improve bioavailability and therapeutics, reduce dose administration and toxic side-effects. Also, self-assembled peptide nanomaterials display such advantages as injectability, biodegradability and biocompatibility. These peptide nanomaterials can be widely applied in drug delivery, regenerative medicine and nanobiotechnology [9]. Dr. Yu reviews the advances of peptide nanomaterials in their physical, chemical and biological aspects. She also discusses their potential applications as drug delivery systems and for their uses in regenerative medicine.

Conventional cancer chemotherapy and radiotherapy are not specific to cancer cells [2]. Novel technologies, such as nanotechnology and tumor immunology, have been used for cancer treatment. Cancer vaccines for cancer treatment can induce immunologic memory, avoid cancer recurrence, toxic side effects, and have high specificity [10]. Dr. Florindo reviews cancer vaccines for cancer treatments. Nanosystems are used for cancer vaccine formulation to increase antigen specificity and immune response. Peptide-loaded polymeric nanomaterials induce a stronger antitumor response at low peptide doses and are a promising platform for peptide-based vaccine delivery. He addresses the applications of nanoparticle tools for cancer vaccines, and the particular characteristics of tumor biology and immunology needed for the design of these nano-delivery tools.

Antibodies, peptides or peptidomimetics are used as targeted drug delivery vehicles [2]. Dr. Belvisi focuses on and addresses the advances in $\alpha_v\beta_3$ integrin-targeted peptide/peptidomimetic-drug conjugates. Integrins are transmembrane receptors and can be bridges for interactions of cell-cell and cell-ECM. Certain ligands of integrin receptors contain tripeptide RGD [11].

Integrins can recognize and bind this RGD motif. Short peptide RGDs as drug delivery vehicles can be coupled with cytotoxic drugs via special linkers, and deliver drugs to targeted sites via interacting with transmembrane receptors integrins.

Gene therapy is the therapeutic delivery of nucleic acid polymers. There are a couple of approved drugs. For example, Glybera has been approved for the treatment of a rare inherited disorder. Peptides also have been used as nucleic acid delivery vehicles [12]. Dr. Kiselev addresses the recent advances in peptides used for transporting nucleic acids. Four cationic amino acids (lysine, arginine, histidine and ornithine) are the components of the peptide-based nucleic acid-binding areas. There are some nucleic acid-binding modules such as lysine dendrimers, arginine-rich modules, lipopeptides and cross-linking peptides. Dr. Kiselev also discusses how to cross membranes by using peptide modules. CPPs can directly penetrate membranes via the interactions between arginine-rich CPPs and the cell membrane, but have no specificity for cell delivery and have a risk of toxicity by nonspecific interactions. In his review, Dr. Kiselev addresses the specificity of nucleic acid transfer and discusses its mediation by ligand modules such as peptide RGD motifs. The peptide-nucleic acid complex is limited to endosomal entrapment. Endosomal escape is mediated by endosome-disruptive modules.

Natural peptides are often poorly stable or bioavailable, and a peptidomimetic strategy can be used to improve enzymatic stability. Peptidomimetics are small molecular compounds and are used to modify or mimic natural peptides by changing the peptide backbones or by replacing natural amino acids with non-natural amino acids [13]. Integrin receptors are overexpressed in many pathological tissues, inhibition of which can be applied to treat some of these diseases. Integrins interact with ECM components. These interactions can be interfered by using small mimetics of integrin-ligand recognition motifs, such as RGD [14]. In his review, Dr. Gentilucci addresses the design and synthesis of peptidomimetic integrin ligands based on heterocyclic-peptide hybrid structures. In another review, Dr. Fregona discusses gold complexes from amino derivatives to peptidomimetics. These peptidomimetics are more stable and more selective against cancer cells and display more potent anti-tumor activity.

REFERENCES

[1] Du, A.W; Stenzel, M.H. Drug carriers for the delivery of therapeutic peptides. *Biomacromolecules,* **2014**, *15*(4), 1097-114.
[2] Sun, L.C; Coy, D.H. Somatostatin receptor-targeted anti-cancer therapy. *Curr. Drug Deliv.,* **2011,** *8*(1), 2-10.
[3] Engel, J.B.; Schally, A.V.; Halmos, G.; Baker, B.; Nagy, A.; Keller, G. Targeted cytotoxic bombesin analog AN-215 effectively inhibits experimental human breast cancers with a low induction of multi-drug resistance proteins. *Endocr. Relat. Cancer,* **2005**, *12*(4), 999-1009.
[4] Fan, T.; Chen, C.; Guo, H.; Xu ,J.; Zhang, J.; Zhu, X.; Yang, Y.; Zhou, Z.; Li, L.; Huang, Y. Design and evaluation of solid lipid nanoparticles modified with peptide ligand for oral delivery of protein drugs. *Eur. J. Pharm. Biopharm.,* **2014**, *88*(2), 518-28.
[5] Kawasaki, E.S.; Player, A. Nanotechnology, nanomedicine, and the development of new, effective therapies for cancer. *Nanomed. Nanotech. Biol. Med.,* **2005**, *1*(2), 101-9.
[6] Lim, S.B.; Banerjee, A.; Onyuksel, H. Improvement of drug safety by the use of lipid-based nanocarriers. *J. Control. Release,* **2012**, *163*(1), 34-45.
[7] Torchilin, V.P. Tat peptide-mediated intracellular delivery of pharmaceutical nanocarriers. *Adv. Drug Deliv. Rev.,* **2008,** *60*(4-5), 548-58.
[8] Jelveh, S.; Chithrani, D.B. Gold nanostructures as a platform for combinational therapy in future cancer therapeutics. *Cancers,* **2011**, *3*(1), 1081-110.
[9] Shi, J.; Xiao, Z.; Kamaly, N.; Farokhzad, O.C. Self-assembled targeted nanoparticles, evolution of technologies and bench to bedside translation. *Acc. Chem. Res.,* **2011**, *44*(10), 1123-34.
[10] Klebanoff, C.A.; Acquavella, N.; Yu, Z.; Restifo, N.P. Therapeutic cancer vaccines, are we there yet? *Immunol. Rev.,* **2011**, *239*(1), 27-44.
[11] Shi, J.; Wang, L.; Kim, Y.S.; Zhai, S.; Liu, Z.; Chen, X.; Liu, S. Improving tumor uptake and excretion kinetics of 99mTc-labeled cyclic arginine-glycine-aspartic (RGD) dimers with triglycine linkers. *J. Med. Chem.,* **2008**, *51*(24), 7980-90.
[12] Kilk, K.; Langel, U. Cellular delivery of peptide nucleic acid by cell-penetrating peptides. *Methods Mol. Biol.,* **2005,** *298*, 131-41.
[13] Ung, P.; Winkler, D.A. Tripeptide motifs in biology, targets for peptidomimetic design. *J. Med. Chem.,* **2011,** *54*(5), 1111-25.
[14] Zanardi, F.; Burreddu, P.; Rassu, G.; Auzzas, L.; Battistini, L.; Curti, C.; Sartori, A.; Nicastro, G.; Menchi, G.; Cini, N.; Bottoncetti, A.; Raspanti, S.; Casiraghi, G. Discovery of subnanomolar arginine-glycine-aspartate-based alphaVbeta3/alphaVbeta5 integrin binders embedding 4-aminoproline residues. *J. Med. Chem.,* **2008**, *51*(6), 1771-82.

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