Short peptide-based smart targeted cancer nanotherapeutics: a glimmer of hope

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First draft submitted: 6 February 2018; Accepted for publication: 12 February 2019; Published online: 26 March 2019

Keywords: cancer nanotherapeutics • functionalization • nanoparticles • peptides • self-assembly • targeted drug delivery

Recent epidemiological data on global cancer incidences and mortality reveals cancer is the second foremost cause of death with a rate of ~1 in 6. In 2018, approximately 9.6 million deaths due to cancer were estimated worldwide [1]. The global cancer burden can be lessened owing to the timely detection and expedient management of cancer patients [2]. Cancer has a higher probability of being cured if diagnosed at the onset and treated effectively. To date, the majority of cancer treatments in the clinical setup involve radiotherapy, surgery and administration of anticancer molecules as chemotherapy, biological therapy or hormonal therapy. However, unwanted toxic effects of radiotherapy and chemotherapy lead to indiscriminate annihilation of healthy cells/noncancerous cells or cause DNA damage/mutation in nonspecific cells with faster multiplication rates in patients' bodies [3]. For example, fast dividing hematopoietic cells, hair follicles, gastrointestinal lining cells and stem cells are observed to cause idiosyncratic side effects post-chemotherapy. Furthermore, emergence of multidrug resistance down the line of chemotherapy deteriorates the quality of a cancer patient's life gradually. To overcome these limitations, targeting anticancer drugs to the tumor site precisely using smart nanoparticle (NP)-based delivery systems is an innovative approach in the field of therapeutic delivery.

NP-based smart drug-delivery systems: a way forward for many conventional treatment regimens

As an alternative strategy to conventional therapies, NP-based drug-delivery systems have been perceived to be promising with higher success rates and superior safety, solubility, bioavailability and pharmacokinetics, as compared with the conventional drug-delivery systems [4]. Recent years have witnessed a substantial surge in the publications, patent applications, preclinical and clinical trials where NP-based drug-delivery systems have been shown to have enriched accretion at the specific tumor site through passive or active mechanisms [5].

Current progress in the development of cancer-oriented nanotherapeutics is comprised of a long list of polymeric NPs such as carbon nanotubes, polymeric micelles, dendrimers, liposomes, polymer drug/protein conjugates, lipid-hybrid systems, polymersomes and peptide-based polymeric nanoparticles. Additionally, inorganic NPs like mesoporous silica NPs, gold NPs, superparamagnetic iron oxide NPs, quantum dots, etc. also embrace great potential in cancer detection and therapy. Various NPs have been tactfully functionalized with different functional moieties to get as far as the target, precisely with improved circulation half-life, intracellular penetration and stimuli-responsiveness, which may be appropriately termed as smart drug-delivery systems [6]. In addition, these functionalized NPs have been reported to succeed in carrier-mediated visualization too. Over the last few

years, usage of these new generation nanocarriers has been gaining popularity in nanotheranostic-based approaches for treating cancer and other diseases [7].

While inclusion of NPs has offered noteworthy progression in cancer treatments, there is cynicism concerning their noxious outcome at cellular and subcellular levels as a result of their completely different physiochemical properties originating at the nanoscale [8]. Even polymeric NPs such as polyacrylates, polymethyl methacrylate, polystyrene, polyacrylamide, etc. have been reported to elicit unwanted toxicity and immunogenicity due to their poor biodegradability [9]. Therefore, switching over to more biodegradable polymeric NPs could be the most pertinent choice with regards to their superior biocompatibility and minimal toxicity. Biodegradable polymers frequently used to construct nanoparticles include materials of natural origin such as gelatin, chitosan, albumin or can be synthetic such as poly(lactic acid), poly(glycolic acid), PLGA poly(lactic-co-glycolic acid) and poly(amino acids).

Peptide-based smart drug-delivery systems: Di- & tri-peptides embrace fascinating flair

During the past decade, significant progress has been made to the use of different peptides as carriers for targeted delivery of diagnostics and chemotherapeutics agents for various cancer types. However, short peptides (di- and tri-peptides) seem to be encouraging, as they are simple in structure, economic, possess superior biocompatibility with enhanced bioactivity and nontoxic/nonantigenic in nature [10,11]. Over the last decade or so, researchers comprehend that short peptides can be a game changer in targeted therapeutic delivery. These peptides can be specifically designed, reasonably synthesized through molecular self-assembly, impeccably functionalized/conjugated to carrier ligands to target specific cell surface receptors and to maximize the therapeutic efficacy of entrapped molecules [12]. Various kinds, such as linear, cyclic, amphiphilic, α -helical and β -sheet peptides can self-assemble to form a variety of nanostructures that includes nanofibers, nanorods, nanotubes, nanovesicles and nanospheres [11]. Several anticancer agents, for example, paclitaxel/docetaxel, fluorouracil, doxorubicin, curcumin have been successfully loaded onto self-assembled peptide assemblies and have been investigated in preclinical and clinical scenarios. In addition, the utility of self-assembling peptides has also been explored as a method for constructing various biosensing devices, as antimicrobial agents and in the field of regenerative medicine [13,14].

Among short-peptides, di-peptides can self-assemble into a variety of ordered nanostructures; hence reduction in fabrication cost is apparent. Research also indicates that di-peptides are advantageous over other peptides as they are very stable under physiological conditions with minimal toxicity/immunogenicity and superior biodegradability. Therefore, di-peptides can be contemplated for diverse biomedical applications involving therapeutic delivery [15,16].

One such dipeptide that first drew attention is diphenylalanine (Phe–Phe), a core motif of the amyloid- β polypeptide fragment, used to generate different nanostructures following self-assembly phenomenon [17]. Phe-Phe motif has been shown to form various nanomorphologies, as well as hydrogels, through self-assembly. Because of their diversified edifice, they are versatile with a multi-application scope in cancer therapy, nanomedicine and biomaterial science. Similarly, the dipeptide arginine- α ,-dehydrophenylalanine that can self-assemble to form well-defined vesicular nanostructures, has been explored for both targeted and pH responsive cancer therapy [18].

One of the most studied tri-peptide is RGD (arginine-glycine-aspartic acid) as it has resilient affinity for integrin receptors overexpressed on cancer cells. There is a plethora of reports that describe RGD-guided nanosystems for cancer therapy. Here are a few recent examples where RGD has been successfully copolymerized with various organic and inorganic entities for precise targeting, loading and controlled release of anti-cancer therapeutics. Recently, Viale *et al.* demonstrated that targeted delivery of doxorubicin through RGD entities complexed with cyclodextrin (binary and tertiary complex) intensified the selectivity and cytotoxicity in A2780 (ovarian), A549 (pulmonary), MDA-MB-231 (breast) and SH-SY5Y (Neuroblast) human cancer cell lines [19]. Similarly, Fang *et al.* demonstrated a higher drug loading efficiency with substantially elevated release of doxorubicin by employing RGD-mounted doxorubicin-loaded biodegradable polymeric micelles in MG-63 osteosarcoma cells under physiological condition [20]. Guo *et al.* reported an increased encapsulation efficiency, superior drug loading capacity and physiological stability using dimeric camptothecin-loaded RGD-PEG-g-poly-L-lysine-b-poly-L-leucine micelles in MDA-MB-231 and MCF-7 breast cancer cell lines [21]. Cilengitide, a cyclic RGD pentapeptide, is in clinical trials for glioblastomas and other tumor management [22,23]. These recent reports clearly indicate that RGD carries a conceivable potential in accelerating anticancer drug delivery to specific targets without fail.

One of the major bottlenecks in cancer treatment is delivering anti-cancer drugs to the desired sites through stromal cells surrounding the tumor. In such cases, delivering prodrugs using peptide-based delivery systems is a novel tactic for successful cancer therapy. Recently, Tsume *et al.* have reported such a prodrug delivery strategy for

gemcitabine (used for pancreatic other cancer treatment) using L-/D-amino acids, and a dipeptide, L-phenylalanyl-L-tyrosine. This approach showed enhanced affinity of gemcitabine to PEPT1 transporter in Caco-2 (human colorectal adenocarcinoma) cells, expedited cellular uptake in human foreskin fibroblast (HFF) cells and inhibited Panc-1 (human pancreatic ductal) cell proliferation with higher specificity and lower toxicity [24].

Considerations & future perspective

Recent publications clearly indicate peptide NPs are one of the extensively explored nanoplatforms, which embrace enormous possibilities in the treatment of cancers and other diseases/disorders. Meanwhile, varied peptide edifices have been realized through self-assembly, an inherent characteristic they exhibit. This property enables their widespread use in several medical and biomedical applications including targeted chemotherapeutics/therapeutics delivery or development of nanotheranostics. However, there are still challenges in understanding as well as envisaging their ordered structures and functions to improve the quality of life of the patients. A multidisciplinary approach would help us to develop innovative and affordable NP-drug formulations or nanotheranostics using these peptides, especially short-peptides, for their effectual clinical applications.

Financial & competing interests disclosure

JJ Panda thanks Biocare grant support, Department of Biotechnology (DBT), Govt. of India, Inspire Faculty Fellowship program of Department of Science and Technology (DST), Govt. of India and core funding from Institute of Nano Science and Technology (INST), an autonomous institute supported by DST, Govt. of India. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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