Title:	Stimuli responsive amino-acid/ peptide/ peptide- metal hybrid nanostructures for site specific anti-canser drug delivery
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Keywords:	amino-acid anti-cancer
Issue Date:	May-2022
Publisher:	IISER Mohali
Abstract:	Cancer is one of the most serious lethal illnesses in today's world and a major health concern after cardiac illnesses in developing countries which does not have any frontier. Cancer has a higher probability of being cured if diagnosed at the onset and treated effectively. Present treatment options for cancer therapy include chemotherapy, surgical therapy and radiation therapy, immunotherapy or either the combination of these therapies. While chemotherapy is a conventional and extensively used treatment method for most of the cancer patients, still it suffers from limitations like fast elimination of the drug molecules, low solubility of most of the chemotherapeutics and drug resistance. Henceforth, nowadays research has been purposed a large proportion to develop cancer therapeutics that can accurately target tumor or cancerous cells, without harming healthy cells. Flourishing since years, self-assembly driven nanostructures are rationally designed with great potential as diagnostic or therapeutic delivery vehicles. For this aim, the present thesis is focused on the development of morphologically different nanostructures starting from a single amino acid to dipeptide to tetrapeptide-based nanostructures as stimuli-responsive therapeutic delivery vehicle in anti-cancer therapy. Very initially, we tried to explore the self-assembly of mere a single amino acid, N-(9-Fluorenylmethoxycarbonyl)-S-trityl-L-cysteine (Fmoc-Cys(Trt)-OH) through microfluidics and manual method. Very interestingly, we observed bowl like formation using microfluidic self-assembly method, whereas through manual method spherical structures were observed. These bowls were further infused into a vesicular shell consisting of amino acid N-(tert-Butoxycarbonyl)-S-trityl-L-cysteine, carrying dual acid labile groups, the triphenylmethyl and the tert-butyloxycarbonyl, to make them pH-responsive system. To illustrate the potential use of the NB-shells in the field of anticancer drug delivery, the particles were loaded with doxorubicin (Dox) with an encapsulation efficiency of 42% and Dox loaded NB-shells exhibited enhanced efficacy in C6 glioma cells and in an animal model of glioblastoma, where the nanoformulations demonstrated significantly higher retardation of tumour volume as compared to free dox. Moving a step further, to develop dual combined chemo-photodynamic- responsive system using bowl shaped structures, doxorubicin-curcumin-amino acid-based composite microbowls (CMBs) were synthesized following miniaturised fluid flow based self-assembly. The CMBs were further exploited as dual chemo-photodynamic therapeutic agents in C6 glioma cells cultured in both 2D monolayer and as 3D spheroids. These CMBs showed synergistic and visible (blue) light sensitive cell-killing effects in both C6 cells and in the 3D spheroids. Further, we tried to develop stimuli- responsive dipeptide (R□F and CF) based self-assembled nanostructures. Firstly, we tried to develop cancer targeted and redox-responsive NPs from disulfide-linked oxidized cysteine-phenylalanine (CF). The NPs were conjugated with folic acid (FA) to specifically target cancer cells and the presence of disulfide bonds would enable the disintegration of the particles in the presence of elevated levels of glutathione (GSH) in cancer cells. We have also demonstrated enhanced uptake of FA derivatized NPs (FA-CFO-NPs) in cancerous cells (C6 glioma and B16F10 melanoma cells) than in normal cells (HEK293T cells), due to the overexpression of FA receptors on the surface of cancer cells. In another dipeptide-based studies, we synthesized NPs from a dipeptide RΔF, containing arginine at the N-terminus and a modified amino acid residue, α, β-dehydrophenylalanine (ΔPhe) at the C-terminus, and determined their responsiveness towards acidic, neutral and alkaline pH (2,7 and 10) conditions. These NPs were loaded with the anticancer drug Dox with a rationale to get a pH-responsive release of Dox specifically into the acidic microenvironment of cancer cells rather than in normal cells to curtail nonspecific toxicity. In-vitro efficacy studies carried-out in various cancer cells revealed that RΔF-Dox-NPs exhibited higher efficacy with 1.65-, 1.95- and 13.34-fold lower IC50 values in comparison to Dox in C6, HCT-116 and AGS cell lines. Starting from a single amino acid self-assembly to dipeptide, we further tried to develop tetrapeptide-based self-assembled auto-fluorescent nanosheets as an anti-cancer drug delivery vehicle. Herein, we reported the synthesis and application of MoS2 exfoliation using peptide-based nanosheets as a multi-modal chemo/siRNA/NIR-responsive drug delivery system in targeting glioma. We developed a hybrid nanosheets as a delivery system acclimatizing Dox and Galectin-1 (gal-1) siRNA to allow NIR-responsive delivery. Various studies have demonstrated that slight change in the morphology, size and surface charge of the nanostructures greatly impact the extent and rate of their cellular internalization efficiency. However, precisely controlling the structural morphology of these nanostructures using different parameters continues to be a key challenge. Moreover, we had also tried to understand the cellular internalization behaviour of morphologically different multi-stimuli- responsive 1D and 2D nanostructures (nanofibers, spherical NPs, nanosheets) originated from a single tetrapeptide molecule. Hence, taking advantage of our morphologically different particles emanating from the same peptide monomer, we ventured on to further explore the intra-cellular fate of our nanostructures. We observed that the nanostructures' cellular internalization is a complex process that gets influenced by particle morphology and this might further affect their intracellular drug delivery potential. Overall, these studies provide initial cues to prepare environment responsive shape shifting peptide-nano assemblies. These studies also provide unique opportunities for undermining specific design criteria to control cellular fate and internalization efficiency of the nanostructures. Thus, in total the assortment of different morphologically tuned stimuli-responsive nanostructures has been developed in this thesis represents a multifaceted combinatorial platform. Such all-in-one anti-cancer combotherapeutic modalities are interesting and superior to many other reported nanosystems in terms of their biocompatibility and ease of fabrication.
URI:	http://hdl.handle.net/123456789/4154
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