Title:	Chitosan derivative based colloidal nanomedicines and hydrogel nanocomposite for combination cancer therapy
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Abstract:	Cancer is one of the crucial health concern and prime cause of death worldwide. It is manifested by uncontrolled abnormal cell growth that can affect any part of body including tissues and bone. Conventional treatment for cancer consists of surgical resection of the tumor followed by chemotherapy and radiation therapy. However, several challenges including incomplete removal of tumor result in cancer recurrence, as well as adverse effects of chemotherapy on normal tissues may limit the outcome of the treatment. Nanomedicine research in oncology is currently progressing at exceptional pace to institute combination drug delivery and multi-modal therapy platforms to overcome the obstacles in conventional treatment. The present thesis is to develop colloidal nanomedicines and a hydrogel nanocomposite based on water soluble chitosan derivates such as glycol chitosan (GC) and carboxymethyl chitosan (CMC) as surface stabilizing agents or three dimensional supporting matrix respectively. The first part deals with assessment of Poly (lactide-co-glycolide) (PLGA) nanoparticles coated in situ with GC and CMC to investigate their physico-chemical characteristics by varying PLGA molecular weight and solubility of the cargo (Paclitaxel or Doxorubicin). It was found that in situ glycol chitosan coating could significantly increase PLGA nanoprecipitation and considerably reduce Extraneous Paclitaxel Precipitates thereby enabling better intracellular delivery of cargo. Taking cue from this, we designed glycol chitosan coated PLGA nanoparticles (gcPNPs) loaded with the drug Lapatinib (LAPA) and further functionalized with porous gold nanoshell (gcPLNS) for photothermal chemotherapy (PTCT). This biocompatible and hemocompatible organo-inorganic combination nanomedicine possessed a photothermal conversion efficiency of ~61%. Combinatorial treatment showed significant breast cancer inhibition (IC50 – LAPA:16μM Vs PTCT: 4.81μM) with enhanced cellular damage manifested by apoptosis. Biodistribution of gcPLNS did not show any obvious toxicity in Balb/c mice for up to 24h post intra venous injection. Considering the negative influence of carrier matrix such as PLGA with drug loading (LAPA in gcPNPs ~6.5%), we further attempted a carrier matrix free organic nanoparticles with combination of a chemotherapeutic drug, LAPA and near infra red absorbing dye, IR820 stabilized with GC. The IR820-LAPA nanoparticles (IR/LNPs) possessed a loading content of ~14 % lapatinib and ~9 % IR820. These organic drug nanoparticles possessed a photothermal conversion efficiency of ~70% with superior photostability. They imparted significant breast cancer cell death compared to single drug nanoparticle controls exclusively in presence of NIR laser. In line with this work, pure drug nanoformulation of lapatinib and doxorubicin was fabricated with ~11.5% and ~15% loading respectively. Here, the combination chemotherapy showed synergism with significant enhancement in cytotoxicity in comparison to single drug nanoformulations. In the final chapater of the thesis, we developed an injectable nanocomposite hydrogel composed of three dimensional biodegradable carboxyl methyl chitosan networks with metal organic framework (MOF) as primary cross linker and magnesium (Mg+2) ions as secondary cross linker. To enhance the functionality of the hydrogel, ultra-small gold nanoparticles (UsGNPs) and anticancer drug, curcumin were incorporated within the micropores of MOF. Due to inter-particle plasmon coupling between UsGNPs, the hydrogel showed significant absorption in near infra red region. The self-healing, NIR responsive hydrogel showed a photothermal conversion efficiency of ~41% and a triggered release of curcumin in acidic pH and imparted significant glioma cell death. All the nano-enabled materials developed in this thesis have an intrinsic potential for dual combination (chemotherapy and/or photothermal) cancer therapy. Further systemic toxicity, biodistribution and therapeutic studies in pre-clinical models would reveal their suitability for clinical translation.
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