DOCTORAL THESIS

Self-assembled Nanostructures for Drug Delivery and Its Surface Modification Method

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Date of Award:
2021

Abstract

In the past decades, nanomedicines have attracted more and more attention due to its outstanding passive targeting property towards solid tumors by EPR (enhanced permeability and retention) effect which enables drugs accumulate more efficiently and prolongs the drug remaining time in cancer tissues. Among these nanomedicines, bio-inert materials were often used as excipients to achieve effective accumulation and passive targeting. These excipients are usually functionless except maintaining the nanostructures of drug delivery system. However, for self-assembled systems, the nanostructures are often maintained by drugs or functional molecules themselves without using excipients which will eliminate concerns of biocompatibility, toxicity and degradability of those carriers.

In chapter one, the background of this research was introduced.

In chapter two, polydopamine coating technique was discussed in great details. In the past, our group had some pioneer works on a self-assembled camptothecin lysine dipeptide conjugate (CPT-KK) which assembles into tubular form with diameters ranging from 80 nm to 120 nm with excellent anticancer activity. However, these CPT-KK tubes are not controllable in size, less stable in super molecular structures and lack active targeting ability. To fix this, we have successfully coated CPT-KK tubes with polydopamine. With polydopamine coating, the length of these tubes was controlled by sonication, the supramolecular structures were stabilized and an interface for antibody binding were also provided which may potentially increase the active targeting ability of these tubes. This polydopamine coating method may also be applied to other self-assembled drug delivery systems for size control, supramolecular structure stabilization and antibody binding.

In chapter three, novel self-assembled rhodamine-based pH responsive materials with excellent fluorescence properties were discussed. Typically, the extracellular pH is 7.3-7.4, the early endosome is ~6.3, the late endosome is ~5.5, and for pH in the lysosome is ~4.7. Materials responding to these exterior pH changes are often used for delivering drug into specific organelles in the cells. At the same time, pH in tumor microenvironments is reported to be more acidic than normal tissues. This encouraged more and more scientists to develop acid responsive materials for anti-cancer drug delivery. Here, two molecules RKK and RKE were designed. Both molecules adopt open-ring form which do not assemble into nanostructures in acidic condition and have a strong emission at 582 nm when excited at 550 nm. However, in basic conditions, both molecules have close-ring form which assemble into tubular form with aggregation induced emission at 454 nm when

excited at 330 nm. pH responsive assembly with different fluorescence mechanisms enables both molecules to be great drug delivery carriers with tracking ability and may potentially be used for delivering drug or genes into living cells.

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